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# BULLETIN
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# SYMPOSIUM ON VAGOTOMY FOR PEPTIC ULCER

## I. Experimental Observations*

HENRY N. HARKINS, DONALD H. HOOKER, T. CRANDALL ALFORD, JR., JOHN CALLANDER, STUART R. ELLIOTT, II, WALTER KEARNS, JR., JAMES MITCHENER, and DENTON A. COOLEY

*From the Department of Surgery, Johns Hopkins University and Hospital, and the Surgical Hunterian Laboratory*

With the current interest in the clinical use of vagotomy for the treatment of peptic ulcer, it is felt that any experimental observations bearing on this subject are pertinent. This is particularly true since many of the older experimental studies involved the use of vagotomy done at other points along the course of the vagus nerves than does the modern clinical procedure.

The present studies can be divided into six groups, three of which directly involve the use of vagotomy and two of which explore the possibility of the use of an anti-histamine drug, benadryl, in the control of experimental ulcer. These six groups of experiments are as follows:

1. An attempt to produce histamine ulcers in the rat.
2. The use of aqueous benadryl solution in an attempt to prevent histamine-in-beeswax ulcers in the guinea pig.
3. The use of benadryl-in-beeswax in an attempt to prevent histamine-in-beeswax ulcers in the guinea pig.
4. The use of vagotomy in an attempt to prevent histamine-in-beeswax ulcers in the guinea pig.
5. The use of vagotomy in preventing pyloric ligation-induced ulcers in the Shay rat.
6. The influence of vagotomy on the development of jejunal ulcers in the Mann-Williamson dog.

These experiments will now be considered individually:

1. ***An attempt to produce histamine ulcers in the rat.*** In a series of four albino rats using larger doses (20 to 80 mgm. of histamine base daily) of histamine-in-beeswax than were used in guinea pigs (see

* Paper given as part of a Symposium on Vagotomy For Peptic Ulcer at the April 14, 1947 meeting of the Johns Hopkins Medical Society.

Section 2), no ulcers were produced after from one to 24 daily injections. These results are compatible with the well known relative immunity of rats towards histamine. Possibly, if the rats had been starved, as they were not in these experiments, ulcers might have formed.

2. *The use of aqueous benadryl solution in an attempt to prevent histamine-in-beeswax ulcers in the guinea pig.* Using the method of Varco, Code, Walpole, and Wangensteen (1941), guinea pigs were given daily subcutaneous injections of histamine-in-beeswax, the usual dose being 5 mg. of histamine base. In a series of 29 guinea pigs, twenty, or 69 per cent, developed peptic ulcers. As shown in Table I, five of seven guinea pigs given similar doses of histamine-in-beeswax de-

TABLE I

*Ulcer Formation in Guinea Pigs Following Subcutaneous Histamine-in-Beeswax Injections: Fifty-Three Successful Experiments*

| PROCEDURE | ULCER OR EROSION FORMATION | PER CENT ULCER |
|---|---|---|
| | | % |
| Control histamine-in-beeswax (H.I.B.) | 20 of 29 guinea pigs | 69 |
| H.I.B. plus benadryl-in-saline per os | 5 of 7 guinea pigs | 72 |
| H.I.B. plus benadryl-in-saline subcutaneously | 8 of 8 guinea pigs | 100 |
| H.I.B. plus benadryl-in-beeswax subcutaneously | 4 of 4 guinea pigs | 100 |
| H.I.B. plus vagotomy | 5 of 5 guinea pigs | 100 |
| Total or average | 42 of 53 guinea pigs | 79 |

veloped ulcer, or 72 per cent, despite the administration of aqueous benadryl solution[1] by mouth (a daily dose of 2 to 4 ml. of benadryl solution; 1 ml. ≡ 10 mgm.).

In additional experiments all of eight guinea pigs (100 per cent) given histamine-in-beeswax plus daily doses of 2 to 3 ml. of benadryl subcutaneously developed peptic ulcers within 2 to 3 days. Seven pigs died with perforated ulcer(s) and the remaining animal died with an unperforated ulcer.

3. *The use of benadryl-in-beeswax in an attempt to prevent histamine-in-beeswax ulcers in the guinea pig.* All four of a series of guinea pigs

[1] Kindly furnished by Parke, Davis and Co.

(100 per cent) treated developed ulcers and died within 1 to 5 days. The daily dosage of benadryl used was 0.1 to 0.4 ml. benadryl-in-beeswax subcutaneously (1.0 gm. benadryl + 1.0 ml. beeswax + 3.5 ml. mineral oil: mix. 1 ml. mixture ≡ 250 mgm. benadryl). Two other guinea pigs died from histamine reactions immediately after injection.

4. *The use of vagotomy in an attempt to prevent histamine-in-beeswax ulcers in the guinea pig.* Infradiaphragmatic section of the vagus nerves was done in a series of guinea pigs under open inhalation ether anesthesia. The immediate mortality of the procedure was high because of the difficulty in adequately exposing the vagi without opening the esophageal hiatus and producing pneumothorax. More latterly this difficulty was somewhat overcome by the use of moist cotton packs around the esophagus. Parenthetically it might be mentioned that this difficulty was not at all a problem in vagotomy on rats (see Section 5, below).

After recovery from the operation, the animals were given the usual daily dose of histamine-in-beeswax and all of five (100 per cent) developed ulcers. Three other guinea pigs developed ulcer, but there was evidence that the vagotomy may not have been complete.

In the entire series of 95 guinea pigs shown in Table II, only 53 were included in the above discussion. The remaining 42 were eliminated because of acute toxicity death (usually from histamine)—25, incomplete vagotomy—3, and operative mortality—14.

5. *The use of vagotomy in preventing pyloric ligation-induced ulcers in the Shay rat.* It has been shown by Shay, Komerov, Fels, and Meranze (1945) that starved rats regularly develop multiple hemorrhagic ulcerations of the gastric rumen, as well as occasional ulcers of the gastric fundus, within 15 hours following pyloric ligation. In a preliminary report, we showed that vagotomy abolishes this tendency to ulcer formation.

*Technic:* Littermate rats weighing about 200 gms were starved for 72 hours, but were allowed water. Operation was performed under inhalation ether anesthesia plus intraperitoneal pentothal (0.6 cc. 1 per cent solution/200 gm. rat). The stomach was exposed through a short vertical epigastric incision using aspetic precautions and the pylorus was ligated in all animals. In the vagotomized half of the series the vagus nerves were completely and tightly ligated

just below the diaphragm. This ligation was done in a manner similar to that used for carotid sinus nerve ligation in Heyman's laboratory, where the ligature surrounded everything but the carotids. In our experiments the ligature surrounded everything in the region except the esophagus. The animals were then replaced in cages without food or water after resuturing the abdominal wound.

*Results:* In the series of rats killed at the end of 24 hours, twenty-two control rats presented an average of 22 ulcers of the rumen per rat. In addition, eight rats had ulcers of the fundus and two had

TABLE II

*Detailed Analysis of All Ninety-Five Guinea Pigs Used in Histamine-in-Beeswax Experiments*

| FINDING | H.I.B. | H.I.B. PLUS BENADRYL-IN-SALINE PER OS | H.I.B. PLUS BENADRYL-IN-SALINE SUBCUTANEOUSLY | H.I.B. PLUS BENADRYL-IN-BEESWAX SUB-CUTANEOUSLY | H.I.B. PLUS VAGOTOMY | TOTAL |
|---|---|---|---|---|---|---|
| No ulcer | 9 | 2 | 0 | 0 | 0 | 11 |
| Erosion | 2 | 2 | 0 | 0 | 0 | 4 |
| Ulcer | 18 | 3 | 8 | 4 | 5(8)† | 41 |
| Acute toxicity death | 10* | 1 | 0 | 3‡ | 11 | 25 |
| Operative mortality | | | | | 14 | 14 |
| Total | 39 | 8 | 8 | 7 | 33 | 95 |

* These animals were not autopsied and some may have had ulcers when death followed other than the initial injection.

† The larger figure includes 3 animals in which the completeness of the vagotomy is doubtful.

‡ One of these three animals was not autopsied.

perforated ulcers. In the series of 20 vagotomized rats, no ulcers were present.

One possible factor in the protective action of vagotomy may be the decrease in the hydrochloric acid content of the stomach contents found at autopsy. In the control series the free acid averaged 34 units and the total acid 94 units, while in the vagotomized group the values were 8 and 66 respectively. The decrease in free acid cannot, however, be the entire explanation of the beneficial effect of vagotomy because in individual experiments 7 vagotomized rats, all without ul-

cer, had a higher gastric acidity than 10 companion control rats, all with ulcer.

Another possible factor in the protective action of vagotomy may be the decrease in gastric volume of the stomach found at autopsy. In the control series, the fluid content of the stomach averaged 15

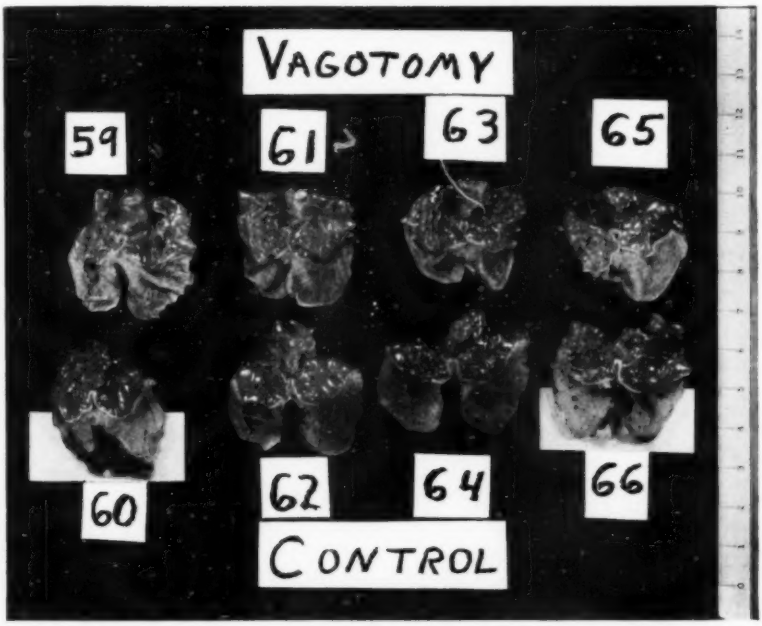


FIG. 1. THE EFFECT OF VAGOTOMY IN PREVENTING PYLORIC LIGATION-INDUCED ULCERS IN THE SHAY RAT

In the upper row, four rat stomachs show no ulcers after the combined operation. In the control stomachs in the lower row, where only pyloric ligation and no vagotomy was done, numerous ulcers of the rumen are present.

ml. while in the vagotomized group it was only 7 ml. This factor alone cannot be the entire explanation of the beneficial effect of vagotomy because in the control series five rats with a gastric volume of 8 ml. or less presented 126 ulcers while in the vagotomized series, seven rats with a gastric volume of 8 ml. or more had no ulcers.

It is of interest that the gastric contents were almost invariably frothy in the vagotomized series whereas in the control animals there was never froth. The factor of swallowed saliva was considered and a series of esophageal ligations was done in addition to the pyloric ligations and in some instances to vagotomy as well. When esophageal ligation was done at the cardia (plus pyloric ligation) only 1 of 7

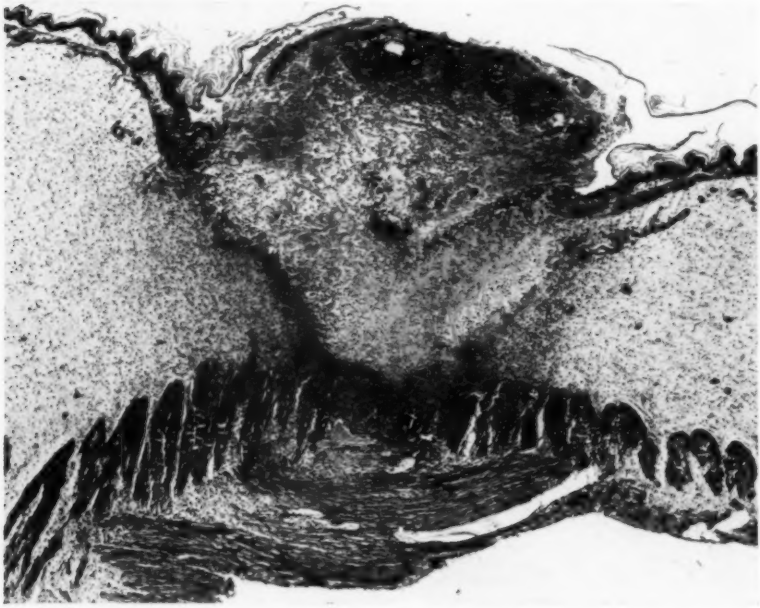

FIG. 2. ULCERATION AND EDEMA OF WALL OF GASTRIC RUMEN 24 HOURS AFTER PYLORIC LIGATION. (× 37½)

rats developed ulcer. The maximum gastric volume was only 1.5 ml.; the free acid 56–80, average 72 units; and the total acid 144–184, average 163. Five other rats were also vagotomized and none of these developed ulcers.

It is soon noted, however, that esophageal ligation at the cardia, even without supplementary vagotomy, invariably produced necrosis of the esophagus up to the level of the tracheal bifurcation, evidently

from interference with the blood supply of the lower esophageal segment. To get around this difficulty esophageal ligations were performed in the neck. One of 6 rats (esophageal ligation in the neck plus pyloric ligation) developed ulcers. The maximum gastric volume was only 6.5 ml.; the free acid 16–80, average 54; and the total acid

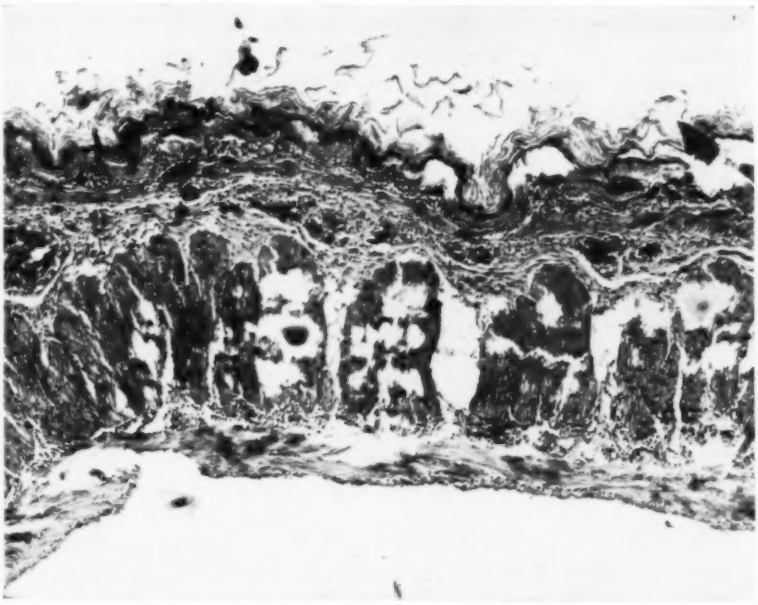

FIG. 3. LACK OF ULCERATION OR EDEMA OF WALL OF GASTRIC RUMEN 24 HOURS AFTER PYLORIC LIGATION IN RAT IN WHICH VAGOTOMY WAS ALSO DONE. (× 62½)

110–204, average 146. Four other rats were in addition vagotomized with no ulcers resulting.

As has been already reported (1947), vagotomy not only prevents ulcer formation in rats with pyloric ligation, but in survival experiments prolongs the life of the animals. In a series of 10 control rats with pyloric ligation, the average duration of life was 49 hours, whereas the series of 10 other rats with additional vagotomy lived an average

of 106 hours. Both groups of animals received intraperitoneal glucose-saline injections. Furthermore, protein analysis of the gastric fluid removed at death indicated such a small amount of protein as to rule out death from acute protein loss.

6. *The influence of vagotomy on the development of jejunal ulcers in the Mann-Williamson dog.*[2] An experiment similating the problem faced by the clinical surgeon and at the same time testing the effect of vagotomy on the development of jejunal ulcer was performed by Beaver and Mann (1931). These authors reported experiments on 6 dogs and found that jejunal ulcers occurred in 100 per cent of their three control animals whereas 67 per cent of the three dogs which had

TABLE III

*Results of Vagotomy in 22 Mann-Williamson Dogs*

| |
|---|
| *13 Controls* |
| 11 developed ulcer (85%) |
| Survival 29–161 days (average = 64 days) |
| 2 died with no ulcer |
| Survival 55–145 days (average = 100 days) |
| *9 with Vagotomy* |
| 1 developed ulcer (11%) |
| Survival 41 days |
| 8 had no ulcer |
| 6 died Survival 28–197 days (average = 118 days) |
| 2 living Survival 263–487 days (average = 375 days) |
| 8 total Survival 28–487 days (average = 182 days). |

been subjected to both the Mann-Williamson operation (1923) and the vagotomy developed ulcers. It is the purpose of this paper to report results to date on a series of 22 dogs prepared similarly to those of Beaver and Mann.

*Technique:* The Mann-Williamson operation (Figure 4) was done according to the principles laid down by these authors. Using aseptic technique, the abdomen was opened through a right rectus incision. The pylorus was divided and the duodenal stump inverted. Approximately 15–20 cm. below the ligament of Treitz, the jejunum was transected, the distal end then being anastomosed to the pyloric end of

[2] The authors acknowledge the assistance of Mr. Thomas Satterfield in this group of experiments.

the stomach and the proximal end being anastomosed to the ileum. End-to-end anastomoses were done whenever possible at the pylorus and end-to-side anastomoses at the lower junction. Continuous fine chromic catgut was used for the mucosal layer and one layer of interrupted or continuous silk for the serosal layer.

The vagotomy was done through the 6th interspace on the left using intratracheal ether anesthesia and a pressure machine. Segments of vagus nerve 1–2 cm. long were removed immediately above the diaphragm and the stumps ligated with silk. An anterior trunk, several small lateral branches and a large posterior trunk were usually demon-

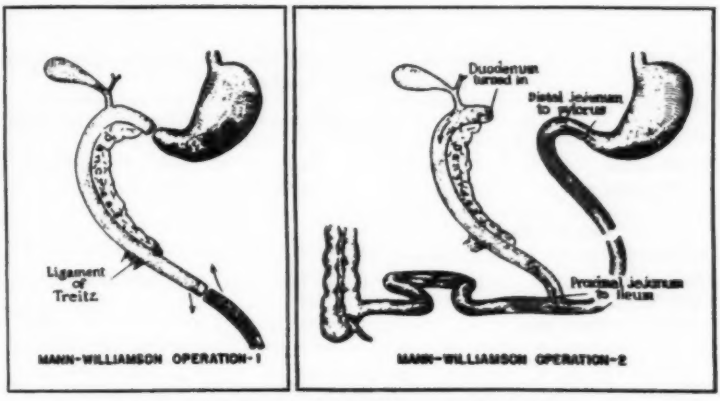


FIG. 4. DIAGRAM OF MANN-WILLIAMSON PROCEDURE

strable. The posterior trunk was made up of a number of small lateral and posterior branches which decussated several centimeters above the diaphragm. The pleural defects, subcutaneous tissues and skin were closed with fine silk. The separation between the ribs was closed by approximating the ribs with heavy braided silk after inflating the lungs with care for it was at this juncture that anesthetic deaths are apt to occur.

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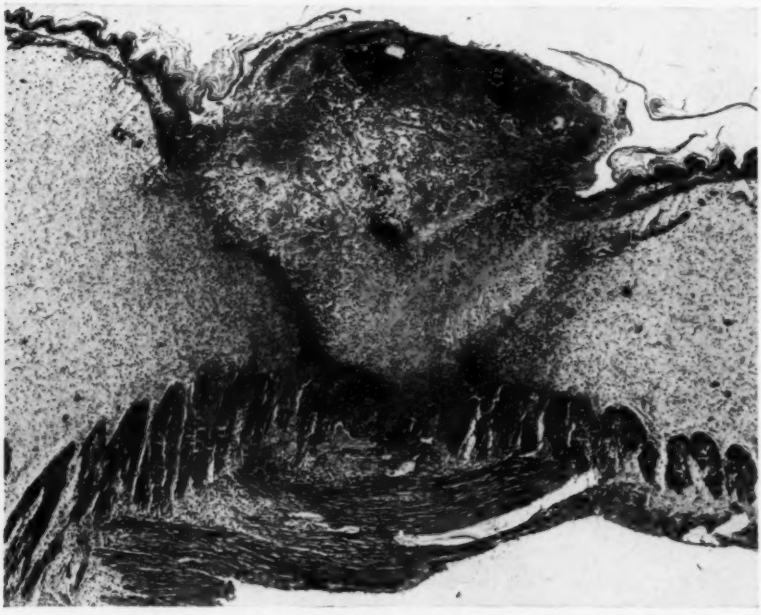

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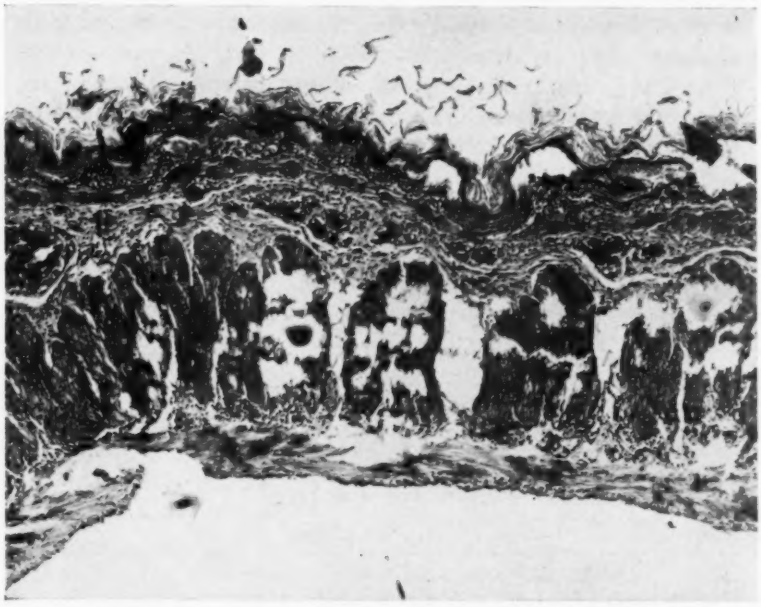

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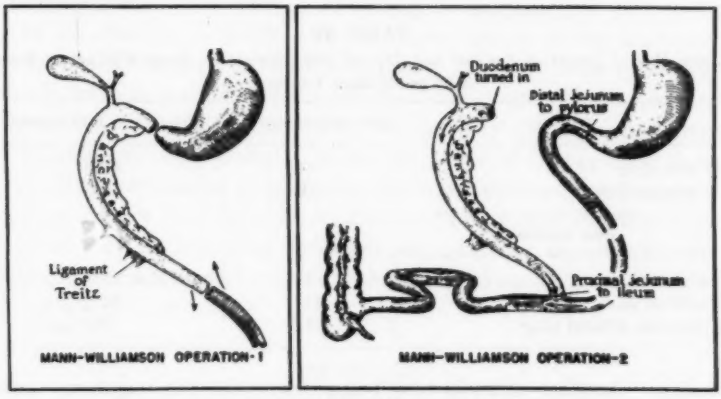


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*Discussion of data:* To eliminate the immediate effects of the operation on the evaluation of the incidence of jejunal ulcer, the dogs reported are limited to those which survived at least 28 days following the Mann-Williamson procedure. It was observed that after the

dogs had recovered from the operation (i.e. several weeks) their general condition improved for a few more weeks. Then they began to lose weight, vigor, and appetite and in this particular series, on an average of 64 days after operation they succumbed to a perforated jejunal ulcer. An effort was made to do the vagotomy as early after the Mann-Williamson operation as possible to eliminate the possibility of error due to the selection of animals which would not have developed ulcer anyway. However, due to distemper and other uncontrollable factors the average time between the Mann-Williamson operation and vagotomy was 51 days. It is interesting that at the time of vagotomy the dogs had already lost, on an average, 16 per cent of their body

TABLE IV

*Correlation of Length of Survival and Loss of Body Weight in Mann-Williamson Dogs With and Without Vagotomy*

| CONTROLS | AVERAGE DAYS SURVIVAL | AVERAGE LOSS BODY WEIGHT |
|---|---|---|
| 11 with ulcer | 64 | 42% |
| 2 without ulcer | 100 | 33% |
| WITH VAGOTOMY | | |
| 1 with ulcer | 41 | more than 35% |
| 6 without ulcer | 118 | 40% |
| 2 probably without ulcer | 375 | 2% (gain) |

weight. Another series is now being done with the vagotomy first to eliminate this possible discrepancy.

Table I shows the control series of 13 Mann-Williamson dogs of which 11 or 85 per cent were proved by autopsy to have ulcer and two not to have ulcer. Of the 11 dogs with ulcer 8 died with a perforation, one was sacrificed, and two died of inanition.

The dogs with ulcer died on an average of 64 days following operation whereas the two without ulcer survived an average of 100 days; one dying 55 days after operation from distemper and the other having been sacrificed 145 days after operation because of severe mange.

The second series is represented by nine dogs which had been subjected to the Mann-Williamson operation and then vagotomy.[3] Six

[3] An additional dog, which had vagotomy performed 95 days before the Mann-Williamson operation and which died 56 days after the latter operation, had no

of these dogs, proven by autopsy to have no ulcer, lived an average of 118 days. Two others are living and well and are therefore presumed not to have an ulcer, having survived 263 and 487 days respectively. The one dog in this series with ulcer died 41 days after the Mann-Williamson operation.

Table II is an effort to correlate the weight loss with the survival time. We find that in the control series the dogs with ulcers lost 9 per cent more weight and their life span was on an average 36 days shorter than those dogs without ulcers. The Mann-Williamson dogs with vagotomy which lost 40 per cent body weight did not have ulcer, and although they lost as much weight as the control dogs with ulcer, the vagotomized dogs lived on an average 54 days longer.

In an attempt to analyze the mortality figures of the thirty-five deaths in one series, we find that eighteen dogs died from peritonitis due to leaks at the anastomoses, one died from evisceration, seven died from infection at the operative site, two died from distemper and seven died from unknown causes. In another series of twenty-eight dogs, nine died from leaking anastomoses, one from infection, one from evisceration, three from gastric retention following the vagotomy, six from anesthesia, four from distemper and four from causes unknown. Roughly one dog out of every four operated on could be used for the summary in Table I.

## DISCUSSION

The absence of protective action of benadryl against histamine-provoked ulcers in guinea pigs agrees with the results of Friesen, Baronofsky, and Wangensteen (1946) who obtained similar results in dogs. This result may be partially explained by an insufficient dosage of benadryl, but is otherwise difficult to understand entirely. On the other hand, the absence of protective action of vagotomy against histamine provoked ulcers can be explained by the peripheral

ulcer at autopsy. Inclusion of this dog in the series gives an ulcer incidence of 10 per cent, an average survival of vagotomy dogs that died of 109 days, an average survival of all vagotomy dogs without ulcer of 155 days, an average body weight loss of 40 per cent and an average interval between the two operations of 56 days.

action of histamine. The protective action of vagotomy against pyloric ligation-induced ulcers is of extreme interest. Peptic ulcer occurred in 85 per cent of the dogs on which the Mann-Williamson operation had been done and in 11 per cent of the dogs on which both the Mann-Williamson operation and vagotomy had been done, but because of the rather long interval between the Mann-Williamson and the vagotomy (i.e. an average of 51 days) the possibility of error due to selection of cases must be considered and the above results viewed with caution.

## CONCLUSIONS

1. Benadryl (per os or subcutaneously; in aqueous or in beeswax-in-oil solution) does not prevent histamine-provoked peptic ulcers in guinea pigs within the limits of dosage and conditions of the experiments reported.

2. Vagotomy does not prevent histamine-provoked ulcers in guinea pigs within the limits of dosage of the drug as used.

3. Vagotomy prevents the development within 24 hours of ligation-induced ulcers in rats and lengthens the life of such animals.

4. Vagotomy lessens the acidity and volume of the accumulated gastric fluid following pyloric ligation in rats, but neither of these factors alone explains the beneficial effect of this procedure.

5. Esophageal ligation, with or without vagotomy, reduces the incidence of pyloric ligation-induced ulcers in rats, but does not entirely prevent them.

6. Vagotomy performed an average of 51 days after Mann-Williamson operations in dogs reduced the incidence of peptic ulceration following this operation from a control level of 85 per cent to 11 per cent.

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# SYMPOSIUM ON VAGOTOMY FOR PEPTIC ULCER

## II. Early Surgical Results in Forty-Three Cases*

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Vagotomy for peptic ulcer has been performed on 43 patients at the Johns Hopkins Hospital. The purpose of this tentative report is to present the early results in these cases, along with certain post-operative observations.

The first operation here was performed just two years ago. It is obvious, therefore, that the post-operative intervals in these studies are not long enough to permit any valid interpretations. Furthermore, this group of patients lacks the clinical and pathologic uniformity requisite to the evaluation of any operative procedure. Vagotomy, either alone or in combination with some other operation for ulcer, has been performed for all the common complications of peptic ulcer. No new or decisive findings are recorded, but the fact that this operation with several modifications has produced interesting and inconstant changes in a varied group of cases would seem to justify an early report.

### CLINICAL MATERIAL

In this series 4 different operative procedures have been used. In order that each of these procedures may be considered separately, the patients are arbitrarily divided into 4 corresponding groups (Table 1). Transthoracic vagotomy with division of the greater splanchnic nerve on one side was performed on 3 patients (Group I) including the first cases in the series. The rationale for this procedure, which was first used here by Dr. William P. Longmire, Jr., was based on the experimental work of Pereira (12), who found a marked vasodilatation of the smaller blood vessels of the pylorus with increase in collateral blood flow to this region following division of the right greater

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splanchnic nerve in dogs. Vagotomy alone (Group II) was done in 16 cases, 5 by the abdominal approach and 11 transthoracically. This group was begun by Dr. Harris B. Schumacker, Jr. in April, 1946. Groups III and IV include patients who have been subjected to some plastic or ablative procedure on the stomach along with vagotomy. Artificial stomata were created in 10 patients (Group III): 8 gastroenterostomies and 2 Finney pyloroplasties. Subtotal gastric resection was performed in 14 cases (Group IV). The amount of

TABLE 1

*Type of Operation*

| GROUP | PROCEDURE | CASES |
|---|---|---|
| I | Vagotomy & Splanchnicotomy | 3 |
| II | Vagotomy alone | 16 |
| | Transthoracic | 11 |
| | Abdominal | 5 |
| III | Vagotomy & Stoma | 10 |
| | Gastroenterostomy | 8 |
| | Pyloroplasty | 2 |
| IV | Vagotomy & Resection | 14 |
| | Polya | 7 |
| | Hofmeister | 7 |
| Total | | 43 |

stomach removed was about 60% on the average. The gastrojejunal anastomoses were of the Polya type in 7 patients and of the Hofmeister type in 7.

The technique of vagotomy was similar to that described by Dragstedt (2, 3, 4, 5, 6), Alvarez (1), and others (15). When the transthoracic approach was chosen, the chest was entered posterolaterally through the bed of the resected left 8th rib or 8th interspace and the supradiaphragmatic esophagus freed of all detectable vagal fibers over a considerable area. The nerves were then divided and the distal ends sutured into the mediastinal pleura usually after resection of nerve segments 2 to 3 inches in length. In the abdominal approach an upper midline incision was used, (the left lobe of the liver reflected

after division of the left triangular ligament) and 2 or 3 inches of esophagus mobilized from above by blunt dissection. The esophagus was then bared of the two vagal trunks, a careful effort being made to include all the ramifications over an area from just above the cardia to the highest proximal point within reach. The free segments of nerve were then resected and the proximal ends sutured into the diaphragmatic peritoneum. In a few cases the ends were allowed to retract far into the mediastinum, after which the esophageal hiatus was carefully peritonealized.

In the entire group of 43, there were 32 duodenal lesions, 9 gastric, and 2 marginal. Of the 9 gastric ulcers, 5 were in the resected group, 1 other was biopsied, and the remaining 3 visualized were grossly benign.

## INDICATIONS

This series embraces, as noted above, most of the complications and complexities of the peptic ulcer problem. The primary indications for surgery in the patients in each group are shown in Table 2. In several cases, of course, additional circumstances, for example, the presence of a gastric lesion, made operation advisable. In over half the cases, ulcer pain constituted the chief indication for surgery. For the most part, this was the so-called uncomplicated pain, either intractible, recurrent and severe, or pain not controlled by the best medical regimen environmentally possible. In 7 of the 8 patients in whom massive hemorrhage or pyloric obstruction were indications, either gastroenterostomy or resection was performed along with vagotomy. There were 9 patients admitted to the hospital for repair of perforations. At intervals of 10 to 14 days following closure of perforation, these patients were submitted to transthoracic vagotomy with the hope that healing of the ulcer would be facilitated and as a safeguard against future difficulty. It is true that while all of these patients had been having ulcer symptoms for variable periods preceding perforation, none would have been considered in need of immediate ulcer surgery other than repair of perforation and probably a few of these could have been carried satisfactorily on medical regimen. One other patient underwent vagotomy at the time of repair of perforation. This was a unique case of ruptured Cushing ulcer occurring a month following removal of a brain tumor in a 6-year-old boy. This

patient lived 2 weeks after vagotomy with apparent resolution of abdominal difficulties and died of meningitis and dural sinus throm-

TABLE 2

*Primary Indications for Vagotomy*

| GROUP | NO. PTS. | PAIN | PERFORATION | OBSTRUCTION | HEMORRHAGE |
|---|---|---|---|---|---|
| I (With Splanchnicotomy) | 3 | 2 | 1 | 0 | 0 |
| II (Vagotomy alone) | 16 | 8 | 7 | 0 | 1 |
| III (With Stoma) | 10 | 7 | 1 | 1 | 1 |
| IV (With Resection) | 14 | 8 | 1 | 2 | 3 |
| Total | 43 | 25 | 10 | 3 | 5 |

TABLE 3

*Location of Ulcer*

| GROUP | NUMBER OF PATIENTS | LOCATION OF ULCER | | |
|---|---|---|---|---|
| | | Gastric | Duodenal | Marginal |
| I (With Splanchnicotomy) | 3 | 1 | 1 | 1 |
| II (Vagotomy Alone) | 16 | 2 | 13 | 1 |
| III (With Stoma) | 10 | 1 | 9 | 0 |
| IV (With Resection) | 14 | 5 | 9 | 0 |
| Total | 43 | 9 | 32 | 2 |

bosis. This is probably the youngest patient on record upon whom vagotomy has been done for ulcer and the only one performed for Cushing ulcer.

## RESULTS

### *1. Follow-up*

With the exception of the 2 patients previously cited in Group I, whom Dr. Longmire operated upon 2 years ago, the patients longest followed in the series are now only 12 months post-operative, the average overall period of study being 6 months. Of the 43 patients on whom vagotomy was performed, 35 have been followed in the Gastro-Intestinal Clinic under the surveillance of Drs. Paulson and Gladsden. Also, detailed questionnaires have been mailed to all patients. In this way, 41 patients have been followed. According to current status, 34 of the 41 have done satisfactorily. In 7 patients the result has been unsatisfactory. The 2 patients not followed were in the group undergoing resection in addition to vagotomy and were both doing well at the time of discharge.

### *2. Symptom Changes*

*A. Pain.* Ulcer pain has disappeared promptly and dramatically in all patients following operation. This effect has been particularly convincing in patients who were experiencing severe pain immediately beforehand. It was noted that the disappearance of pain has enabled many of these people to surmount the usual post-operative difficulties with uncommon ease and speed. In the unsatisfactory group, 3 patients experienced recrudescence of ulcer pain along with reactivation of their ulcers after periods of 5, 10, and 11 months. Of these, 2 underwent right major splanchnicotomy at the time of vagotomy and subsequently showed evidence that all the vagal fibers had not been divided. There are 3 other patients in the unsatisfactory group who have complained of abdominal discomfort, but in these cases the pain has been that of gastric dilatation and not ulcer pain. Excepting 2 patients in Group IV who have noted occasional mild twinges of abdominal pain, none of the patients followed in Groups III and IV have experienced pain.

*B. Vomiting.* Despite the fact that continuous gastric suction was used routinely for the first 2 or 3 post-operative days, 9 patients experienced considerable vomiting while still on the surgical wards. Such episodes were related to the gastric atony and dilatation which

characteristically followed vagotomy and not to preoperative symptomatology. This early vomiting is a post-operative complication which can be controlled and probably prevented by adequately prolonged continuous removal of gastric contents followed by carefully graduated diet. Only 2 patients in the satisfactory group have been troubled with vomiting since discharge. One of these had to be readmitted 3 weeks after operation for gastric decompression. In both, the difficulty disappeared within a month after operation.

Of the 6 unsatisfactory cases with troublesome post-vagotomy vomiting, 4 have come to reoperation. Active peptic ulceration was present in 3 of these cases, 2 being the incompletely vagotomized patients in Group I and the third, a man resected 5 months after thransthoracic vagotomy, whose denervation was complete according to the insulin test. The fourth patient had an atonic stomach, but the ulcer had healed. No sign of pyloric obstruction was present in any of the 4 cases. In fact, in 3 patients having clinical and roentgenological signs compatible with a diagnosis of pyloric stenosis, the pyloric rings were palpated carefully at reoperation and were found to be free and patulous, the stomachs atonic and dilated, and, in 2 cases, the proximal portions of the duodenum somewhat larger than normal. It should be said that one of these patients, despite the absence of organic obstruction, had been shown to have slight impairment of gastric motility and emptying even before vagotomy, although vomiting was never present until afterward. Resections were performed on the 3 patients with active ulcers and a gastroenterostomy on the patient with gastric dilatation. All are now doing well. In the unsatisfactory group, 2 other patients, now 10 and 4 months after vagotomy, are having troublesome vomiting.

*C. Hemorrhage.* Before operation, 16 patients gave a history of significant bleeding, massive hemorrhage being the chief indication for surgery in 5 of these. There has been no proved instance of hemorrhage in any patient following vagotomy, although 2 patients gave a history of having had small tarry stools 7 and 8 months post-operatively.

*D. Fullness after Eating.* Transient post-prandial distress has been common as a post-operative complaint present to varying degrees in 29 patients. This symptom usually disappeared or abated

greatly within the first month, though at the present time 22 patients state that they are aware of occasional, mild fullness, especially after overeating. Except for patients in the unsatisfactory group, in 6 of whom severe post-prandial fullness was added to their other troubles, this symptom has not been a real problem. Dietary limitations have been advised in the group with resections and in other patients only as needed to control symptoms of fullness. Under this policy, there are now 22 patients eating everything and 11 patients on frequent-feeding regimens, the latter group including those with resections or

TABLE 4

*Changes in Bowel Habits and Weight following Vagotomy*

| GROUP | NO. OF PATIENTS | INCREASED DEFECATORY RATE | DIARRHEA | AVERAGE WEIGHT GAIN |
|---|---|---|---|---|
| | | | | *pounds* |
| I (With Splanchnicotomy) | 3 | 0 | 0 | 0 |
| II (Vagotomy Alone) | 16 | 16 | 4 | 19 |
| III (With stoma) | 10 | 9 | 2 | 16 |
| IV With Resection | 14 | 8 | 2 | 13 |
| Total | 43 | 33 | 8 | 15 |

others in the early post-operative period. The incidence of dietary limitation is greater (64%) in the resection group than in the satisfactory cases in the other groups (17%). This rather high figure includes all patients dieting and does not represent the true incidence of digestive cripples since feeding restrictions have been advised in some cases in the absence of symptomatic indications.

*E. Bowel Habits.* 33 patients experienced a post-vagotomy increase in their daily defecatory rate. Since 26 patients had constipation before vagotomy, this abrupt change, in most instances, has proved salutory. However, 8 patients were bothered with diar-

rhea for post-operative periods of 4 to 12 weeks. This consisted usually of 5 to 10 soft or semi-solid stools a day, typically as diarrhea after eating, and has been controlled satisfactorily by the use of pavetrine and phenobarbital. At present, one patient who had vagotomy with gastroenterostomy 3 months ago is having severe diarrhea. Despite diarrhea, weight gain has been uniformly striking.

*F. Attitude.* Particularly striking has been the enthusiasm of the patients themselves about the operation. The absence of pain seems to be the key to this fact, since even those having diarrhea and post-prandial fullness tend to minimize these complaints in expostulating over their freedom from ulcer pain. All patients state that they would go through the operation again, knowing what they now know, with the exception of one man now doing well, whose objection was the many "tubes and needles" he had to cope with in the hospital.

### *3. Secretory Changes*

The changes in gastric secretory function which have followed vagotomy are presented in an accompanying article by Drs. Paulson and Gladsden in their studies on patients followed in the Gastro-Intestinal Clinic. All groups have shown a considerable reduction in the volume of 12-hour resting secretion and in the concentration of free HCl in the unstimulated stomach. The insulin test (9, 10), in which hypoglycemia is induced as a stimulus to vagogenic gastric secretion, has been employed in 21 patients. While the post-vagotomy patterns with this test have generally indicated absence of vagal influence on the stomach, the results in several cases have been equivocal. It is obvious that the intra-gastric reflux of duodenal and jejunal contents through a gastroenterostomy makes the interpretation of the insulin test in Groups III and IV extremely difficult.

### *4. Roentgenological Changes*

Vagotomy has produced some degree of motor paralysis of the stomach with resulting atony and dilatation and prolonged retention of gastric contents by x-ray in 67% of all the patients studied. Thus, of the 36 patients who had careful pre- and post-operative x-ray studies of gastric function, 24 showed this post-vagotomy gastroplegia, the incidence being lower in the resected group than in the other groups.

It must be pointed out that this figure for gastric paralysis represents x-ray findings and is considerably less than the true incidence of post-vagotomy gastroplegia. The gastric decompression used in the early post-operative period probably contributed to the apparently normal gastric motility seen roentgenologically in 12 patients.

The gastric dilatation and atony characteristically appeared immediately after operation, and, in 10 cases, was first manifested clinically even before the routine post-operative x-rays could be obtained. The usual signs were epigastric discomfort with a palpably enlarged stomach or profuse vomiting of old and foul gastric contents, despite the 48 to 72 hours of continuous suction used routinely in these cases. Typically, this severe loss of function produced by vagotomy, parallels the diminution of secretory activity. In all the satisfactory cases there has been a gradual return of motility and gastric emptying after periods of 6 to 12 months; at present, 6 patients whose stomachs were previously paralyzed have regained complete 5 hour emptying. It is difficult to explain why 3 patients whose post-operative insulin tests showed complete absence of vagal secretory function did not suffer any motor loss whatever.

Of the unsatisfactory cases, 5 have shown persistent gastric retention and dilatation, and 3 of these at reoperation were found to have widely patulous pyloric rings, with only the gastric atony and paralysis to account for their profound gastric retention. The presence of a gastroenterostomy or pyloroplasty seemed to have no effect on the immediate post-vagotomy development of intra-gastric stasis, gastric dilatation and retention, 9 out of 10 cases in this group suffering this alteration of function in the early post-operative period. For the first month the new stoma may not even be seen fluoroscopically to function at all. Once the stomach begins to regain its tone, however, such an artificial opening does prove helpful in hastening the return of motility. The apparent reasons for this in gastroenterostomy are (1) the presence of two exits for food instead of one and (2) the fact that the gastroenterostomy not only has the mechanical advantage of gravity, but may also transmit materials propelled by the weak and incomplete contractions seen in the upper half of the palsied stomach, which would be ineffective in emptying food through the pylorus.

### *5. Failures*

The 7 cases with unsatisfactory results following vagotomy are summarized diagrammatically in Table 5. In an evaluation of vagotomy, the two patients whose operations were complicated by splanch-

TABLE 5

*Unsatisfactory Cases*

(Failures)

| CASE NO. | INDICATION | PROCEDURE | RESULT | OUTCOME |
|---|---|---|---|---|
| 1. J.R. | Perforated gastric | Vagotomy and right splanchnicotomy | Severe retention and recurrent ulcer pain in 10 mo. | Satisfactory after resection |
| 2. J.B. | Pain | Vagotomy and right splanchnicotomy | Recurrent ulcer with pain in 11 mo. | Satisfactory after resection |
| 3. W.A. | Perforated gastric | Vagotomy and repair perforated Cushing ulcer | Died p.o. 14 of meningitis and dural sinus thrombosis | |
| 4. E.R. | Pain | Vagotomy, transthoracic | Severe retention, recurrent ulcer with pain in 5 mo. | Satisfactory after resection |
| 5. J.H. | Pain, gastric | Vagotomy, abdominal, biopsy gastric ulcer | Severe retention, dilitation of stomach in 6 mo. | Satisfactory after gastro-enterostomy |
| 6. L.O. | Perforation | Vagotomy, transthoracic | Fullness, vomiting, gastric atony | Unsatisfactory |
| 7. H.R. | Pain | Vagotomy, transthoracic | Fullness, vomiting, weight loss, gastric atony | Unsatisfactory |

nicotomy and the child with Cushing ulcer who died as a result of his brain operation must be excluded. This leaves 4 patients with unsatisfactory results. Two of these have undergone subsequent operations, one for recurrent ulcer, the other for gastroplegia of vagotomy. The other two are suffering with symptoms of this gastric atony and may also need another operation.

## COMMENT

In this series 8 duodenal ulcers have been treated by transthoracic vagotomy performed 10 to 14 days after closure of perforations; 7 of these patients are now symptomless and the 8th is suffering a degree of gastric retention and atony which may need gastroenterostomy. While patients with perforations can expect continued ulcer difficulty which will necessitate subsequent surgery in over one-half the cases, the indication for this seemingly prophylactic procedure may be questioned. The answer to this, of course, may not be known for many years. It is fair to say that this group has done exceedingly well so far. The transthoracic operation has the advantage over other procedures of avoiding the contaminated or potentially contaminated field through which the perforation has been closed. The operation is performed during the same hospital stay and at a time after perforation when the patient is in good condition. The perforation repair facilitates inspection of the lesion and performance of a gastroenterostomy when one is indicated, thus dispelling the usual objection that transthoracic vagotomy does not allow investigation of the lesion being treated. Another advantage of such a scheme is the fact that a complete vagotomy is more readily and certainly accomplished when the esophagus is approached from above rather than below the diaphragm.

It is difficult to explain the apparent disparities between gastric secretory and motor loss in patients following vagotomy. These two functions, in so far as they represent the vagal or cephalic phases of gastric digestion, are characteristically diminished to comparable degrees after operation, but the relationship between these two factors is by no means constant. Three patients who had complete loss of vagal secretory response, as measured by the insulin test, showed no gastric motor abnormality by x-ray. The one patient with recurrence of his ulcer following complete vagotomy continued to show marked symptomatic gastric retention and atony until the time of resection, although a second insulin test performed just before resection gave an equivocal secretory response, suggesting partial reactivation of vagal secretory function. More confusing is one patient with a dramatic result, now followed over 12 months, who shows no impairment of vagal secretion or motility on repeated examination.

Such bizarre results are not common, but they do occur and are

noted or reported by Dragstedt (4, 5, 6), Grimson (7, 8, 14), Moore (11) and others. Undoubtedly more than one factor is responsible for such variations on the general rule. Anatomically incomplete vagus section, the inconsistency of the insulin test and the fact that section of all vagal fibres is not always necessary to effect an apparent cure (14), these three factors play a role in confusing the picture.

Vagotomy performed without any other procedure has produced unsatisfactory results in 4 of the 15 cases. This is a high incidence of failure, 27% within the first year, for any operative procedure for ul-

TABLE 6

*Overall Results in 41 Patients Followed*

| GROUP | NO. OF PATIENTS | SATISFACTORY | UNSATISFACTORY |
|---|---|---|---|
| I (With Splanchnicotomy) | 3 | 1 (33%) | 2 (67%) |
| II (Vagotomy Alone) | 16 | 11 (69%) | 5 (31%) |
| III (With Stoma) | 10 | 10 (100%) | 0 |
| IV (With Resection) | 12 | 12 (100%) | 0 |
| Total..... | 41 | 34 (83%) | 7 (17%) |

cer. Of these 4 patients, 2 have since been relieved by subsequent operations on the stomach. The 2 remaining patients should be susceptible to similar relief.

While the role of vagotomy in ulcer therapy is by no means clearly established, we believe that there is sufficient evidence in its favor to justify further clinical trial in selected cases. Occasional failure of vagotomy to heal an ulcer apparently does occur, leaving the patient a candidate for gastric resection. Oftener the gastric motor effect of vagotomy will necessitate a future plastic operation on the stomach, the ulcer having healed satisfactorily. In fairness to the procedure, it must be emphasized that vagotomy does not contraindicate or add

difficulty to further surgical procedures on the stomach. This is a virtue which other operations for ulcer cannot claim.

## SUMMARY

1. Vagotomy, either alone or in conjunction with another operative procedure, has been performed on 43 patients with peptic ulcer. One post-operative death occurred, but this was not related to vagotomy.

2. The clinical results in the 41 patients followed 2 to 24 months have been satisfactory in 34 cases or 83%, and unsatisfactory in 7 cases or 17%. Excluding the one patient who died with complications of craniotomy and 3 patients in whom vagotomy was compli-

TABLE 7

*Corrected Results in 37 Patients*

(Omitting 1 pt. with Cushing ulcer and 3 pts. with Splanchnicotomy)

| GROUP | NO. OF PATIENTS | SATISFACTORY | UNSATISFACTORY |
|---|---|---|---|
| II (Vagotomy alone) | 15 | 11 (73%) | 4 (27%) |
| III (With Stoma) | 10 | 10 (100%) | 0 |
| IV (With Resection) | 12 | 12 (100%) | 0 |
| Total | 37 | 33 (89%) | 4 (11%) |

cated by simultaneous division of one splanchnic nerve, the corrected results are: 37 patients followed with no mortality; satisfactory results in 33 cases, or 89%, unsatisfactory in 4 cases, or 11%. The 2 patients lost to the follow-up were doing well at the time of discharge.

3. In the satisfactory group, the disappearance of ulcer pain has been most striking and has overshadowed other troublesome, though transient, effects of vagotomy. These in order of frequency, have been: (1) an increase in the number of daily stools with occasional diarrhea; (2) post-prandial fullness and (3) occasional post-operative vomiting, the latter two effects being related to the motor paralysis of the stomach which followed vagotomy in 24 patients or 67% of those studied.

4. In the unsatisfactory group, 2 patients have come to reoperation, one for recurrence of ulceration and one for intractible gastric retention and dilatation due to vagotomy motor paralysis. There are 2 patients in this group who have continued to show uncontrollable signs of severe gastroplegia and who may need gastroenterostomy in the future.

5. All the failures were in patients who had vagotomy without any additional operative procedure, either plastic or ablative, on the stomach itself. The results have been uniformly satisfactory in the 24 patients undergoing some such procedure in addition to vagotomy. Most satisfactory of all have been the 10 patients in Group III who had gastroenterostomy or pyloroplasty along with vagotomy.

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# MEDICAL ASPECTS OF VAGOTOMY FOR PEPTIC ULCER[1]

## Including Observations on the Clinical Value of the Insulin Test and on Post-Operative Criteria for the Completeness of Bilateral Gastric Vagus Section

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[1] Paper given as part of a Symposium on Vagotomy For Peptic Ulcer at the April 14, 1947 meeting of the Johns Hopkins Medical Society.

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VI. Problems associated with Vagotomy
A. New Situations Arising from Absence of or Obtunded Pain
B. Gastritis and Jejunitis (Gastroscopic Evidence)
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## INTRODUCTION

In an attempt to modify the acid factor especially in the empty stomach, this being regarded as an important consideration in the etiology of many peptic ulcers, vagotomy was re-introduced and made technically practical by Dragstedt and Owens (2).

Enthusiasm for the procedure in some quarters; the wide interest in medical circles; the natural concern of patients with this disease as to what the new operation has to offer, this being stimulated by descriptions and reports in the lay press; and the possibility that it may materially alter our approach to the problem of management —all of these make it highly advisable not only to evaluate our early experiences with vagotomy in peptic ulcer, but to continue to do so over a period of years, since its final place may not be determinable until then.

## RATIONALE

### *Complete severance of gastric vagal branches for relief of peptic ulcer*

The acid in the gastric secretion is regarded by many as the proximal cause of a large number of peptic ulcers (3,4). As classified by Ivy (5) there are three phases of gastric secretion: gastric, intestinal and cephalic. The first two phases are stimulated and at the same time buffered and diluted by food. The stimulation of the cephalic or psychic phase is independent of food in the stomach and intestines. It is stimulated by the emotions (6) and other sensory phenomena as olfactory, gustatory and ocular impulses which are transmitted to the stomach from the medullary center by way of the vagus nerve, as originally pointed out by Pavlov (7). Under these circumstances the acid may be unbuffered and undiluted, this occurring particularly during the nocturnal hours. Hence, the corrosive action upon the gastric and duodenal mucosa is greater. Therefore, it was hypothe-

sized that complete bilateral section of vagal branches supplying the stomach should abolish this type of secretion hence facilitating ulcer healing and preventing recurrences. For greater detail one is referred to the papers of Dragstedt and his numerous co-workers (2, 4, 8, 9, 10, 11). An important by-product of such a procedure is profound alteration in gastric tone and motility—gastric dilatation and marked diminution of peristalsis or peristaltic inertia.

## MATERIAL STUDIED

The cases have been divided into four groups:

I. Vagotomy alone or following previous (10 to 14 days) suturing of a perforated peptic ulcer: total of 14 cases
   A. Supradiaphragmatic vagotomy: 11 cases
   B. Infradiaphragmatic vagotomy: 3 cases
II. Vagotomy, infradiaphragmatically, with stoma: total of 10 cases
   A. Gastroenterostomy: 8 cases
   B. Pyloroplasty: 2 cases
III. Vagotomy, infradiaphragmatically, with subtotal gastrectomy: 15 cases
IV. Vagotomy with splanchnicectomy

Our data will be somewhat at variance with our surgical colleagues at the Johns Hopkins Hospital because we are eliminating the fourth group—vagotomy with splanchnicectomy. (See Johns and Grose (12)). Theoretically, these systems—sympathetic and parasympathetic—are, in a general way, considered as antagonistic and under normal circumstances are in a state of balance (13), thus tending to further complicate evaluation of vagotomy. Therefore, only the first three groups will be considered.

Group I. *Vagotomy alone or following previous (10 to 14 days) suturing of perforated ulcer (14 cases):* Six of these patients came to the hospital for treatment of acute perforation of peptic ulcer. These were sutured immediately and after ten days to two weeks a supradiaphragmatic bilateral vagotomy was done. The purpose of the latter operation was to protect against recurring symptoms with or without ulcerations since 50% to 82.5% of this group from three to five years following simple suturing present recurrences and other difficulties (14, 15, 16, 17). Of the other eight cases, three were done infra-

diaphragmatically and five supradiaphragmatically. These eight, (without previous perforation), were done because of persistent complaints over long but varying periods in which medical management was said not to be helpful and which interfered with routine daily activities. The past history was characterized by pain of varying degrees, heart-burn and gnawing, and many had previous episodes of gross hemorrhage. The duration of symptoms was from three months to ten years. Four had ulcer craters, and four manifested deformed caps and gave definite histories of previous attacks of melena.

Group II. *Vagotomy with Stoma (10 cases)*: All cases in this group had infradiaphragmatic vagotomy, two with pyloroplasty and eight with gastroenterostomy. Symptoms varied from one to thirty-seven years, and again pain was the outstanding feature in all but one who had nausea and emesis without retention, but with x-ray evidence of duodenal ulceration. Only three of this group had definite obstruction prior to operation. Here, too, vagotomy was done for relief of the ulcer and the gastroenterostomy or pyloroplasty to prevent the frequent sequelae of the operation: dilatation and retention, which is reported by Grimson and his co-workers (18), and Dragstedt and Schafer (10), and Winkelstein (19) as being of sufficient import in about 20% of cases following simple vagotomy to require additional surgery for its relief.

Group III. *Vagotomy with sub-total gastric resection* (15 cases): Indications usually were either recurrent hemorrhage or gastric ulcer. Obstruction was encountered in two and pain was pronounced in four prior to operation. Symptoms varied from one to twenty-three years.

## RESULTS

I. *Symptoms: Pain:* Immediately following operation, the above-mentioned symptoms no longer manifested themselves in thirty-six of the thirty-nine patients observed over varying periods up to a year which represents this period of study. The most striking subjective change was complete cessation of pain. In three of the fourteen cases in Group I, distress recurred within a few months after operation; in one it was associated with marked retention and relieved by gastroenterostomy; in another, evidence of ulceration as well as distressing fullness persisted after four months and was satisfactorily treated by

subtotal gastric resection; and in the third case, no further studies were permitted by the patient to account for the return of pain, nausea, emesis, loss of weight and tarry stools.

*Fullness:* All of the cases in Group I (vagotomy without pyloroplasty, gastroenterostomy or sub-total gastrectomy) complained of varying degrees of fullness. In only two instances, thought to be due to gastric paralysis following operation, was further surgical intervention necessary. However, in the others, as time went on, this symptom became much less pronounced.

*Nausea and emesis:* This occurred only on rare occasions for short periods after hospital discharge. Often it was regurgitation rather than emesis. This was ascribed to the gastric dilatation, atony and peristaltic inertia.[4] These complaints eventually disappeared.

*Appetite:* All experienced hunger sensations. This resulted in a remarkable gain in weight in most instances.

*Defecation:* A change in bowel habit was noted. Previous to operation, all were constipated. Following operation, nearly all had one to three well formed movements daily. In a few, shortly after operation, there was diarrhoea for brief periods which was readily controlled by simple measures, or was relieved spontaneously. After a few months, this was not present in any case.

*Ability to work:* All patients (except the three cases presenting post-operative problems in Group I referred to above) spoke of increasing vigor and their ability to do a full day's work.

*Chest pains at operative site:* In those in whom transthoracic vagotomies were done, there was pain at the site of the chest incision which usually subsided in a few weeks.

II. *Signs: X-rays:* A characteristic phenomenon of bilateral vagotomy is gastric dilatation, atony and peristaltic diminution or inertia. All of these factors are not always present and they are not always interrelated. Sometimes there is dilatation and the motility is rela-

[4] Control of this problem was facilitated by the use of Urethane of B methylcholine chloride (Urecholine-Merck). A 5 mgm. tablet is given three times daily, one hour before eating. This has been administered indefinitely without untoward reactions. Apparently this cholinergic agent stimulates vagal nerve endings and results in better gastric emptying. We are indebted to Dr. Augustus Gibson of Merck & Company, Inc., Rahway, N. J., for his cooperation.

tively satisfactory. The reverse situation is also seen. A few almost immediately following vagotomy manifest normal tone and motor function. In many, the stomach tends to assume normal tonicity and activity by the end of the first post-operative year confirming the observations of Moore, Chapman, Schulz and Jones (20). Details are also enumerated by Johns and Grose (12).

*Gastroscopic appearances:* In those without gastroenterostomy and sub-total resection, there is virtually no change in the gastric mucosal pattern. However, the stomach is less active than that usually encountered. The antrum appears relatively patulous and there is lessened peristaltic activity; this might be expected in view of interference with the vagal innervation of the stomach. The unusual finding is the tendency of the pyloric sphincter to remain more or less open except when a peristaltic wave rushes over it momentarily following which it reverts to relative patulousness. This is not unlike that seen in an occasional case without vagotomy but which has been saturated with an anti-spasmodic. However, these findings are contrary to what is noted—gastroscopically—in the untreated and non-vagotomized stomach where the antrum is of better tone and the sphincter seems closed for the most part, visualization of the latter being difficult and momentary. To what extent the resumption of normal tone of the antrum and pyloric sphincter is to be seen gastroscopically in those with vagotomy at a later date, remains to be determined. Incidentally, these gastroscopic findings following vagotomy are in line with those which surgeons encountered during re-operation following previous vagotomy. In vagotomy with gastroenterostomy, some negligible mucosal changes may be seen. But here, too, the antrum and the pyloric sphincter are as above described. In sub-total gastrectomy, the oedema, thickening and nodular-like hypertrophy, with or without erythema and friability, as noted in similar instances without vagotomy (21) are also seen (see Figs. 1 and 2). As far as we know these findings have not been recorded elsewhere; this problem will be discussed further in a subsequent communication.

III. *Complications:* To date—within one year following operation —only three presented problems. These were among fourteen in Group I already referred to.

IV. *Disturbance of other organs:* An attempt was made to study the

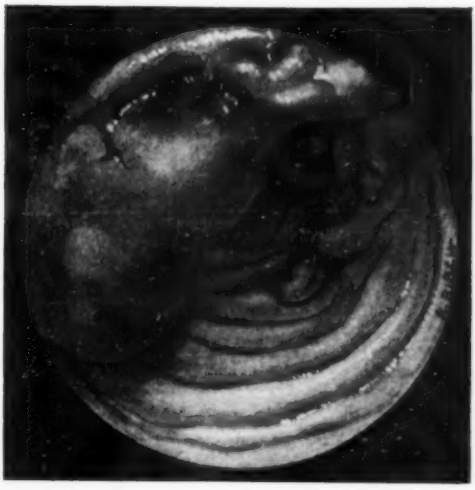


FIG. 1. Nine months after vagotomy and subtotal gastric resection: nodularity, hypertrophy, friability and erosion of residual stomach as well as thickening with irregularity of contiguous jejunal folds. (Case Y).

FIG. 2. Three months after vagotomy and subtotal gastric resection: oedema, erythema, ready friability and bleeding of the residual stomach with a thinning out of contiguous jejunal folds (Case X).

TABLE 1

*Pancreatic Ferments in the Serum Before and After Vagotomy*

| CASE | OPERATION | AMYLASE* | | | LIPASE† | | |
|---|---|---|---|---|---|---|---|
| | | Before operation | After operation | | Before operation | After operation | |
| | | mgm.% | mgm.% | Days | cc. | cc. | Days |
| 1. F.S. | Subdiaphragmatic vagotomy with gastroenterostomy | — | — | — | 0 | 0.3 | 17 |
| 2. L.V. | Suture of perforation followed by transthoracic vagotomy | 342 | 366 | 11 | — | — | — |
| 3. W.M.R. | Subdiaphragmatic vagotomy with subtotal resection | 198 | 445 | 9 | — | — | — |
| 4. W.L. | Subdiaphragmatic vagotomy with subtotal resection | 202 | 132 | 9 | 0 | 0.4 | 13 |
| 5. J.D. | Suture of preforation followed by transthoracic vagotomy | 194 | 162 | 9 | 0.4 | 0 | 26 |
| 6. H.R. | Subdiaphragmatic vagotomy | 122 | 302 | 10 | — | — | — |
| 7. P.T. | Suture of perforation followed by transthoracic vagotomy | 230 | 132 | 7 | 0 | 0.1 | 7 |
| 8. R.W. | Suture of perforation followed by transthoracic vagotomy | 248 | 127 | — | — | — | — |
| 9. W.C. | Subdiaphragmatic vagotomy with gastroenterostomy | 254 | 232 | — | — | — | — |
| 10. F.M. | Subdiaphragmatic vagotomy | — | — | — | 0.7 | 0 | — |

* Myers, V. C., Freed, A. H., Rosinski, E. A.: J. Biol. Chem., **154.:** 39, 1944. Normal values—90–280 mgm.% reducing substance.

† Todd, J. C., and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods. Philadelphia and London, W. B. Saunders Co. Ed. X, 1945, p. 435. Normal values—0–1.2 cc. N/20 NaOH.

influence of vagotomy on pancreatic ferments (see Table 1). In two cases (3 and 6) elevations in serum amylase occurred subsequent to this operation, and in one case (case 2) this enzyme was elevated both before and after vagotomy. In five, this determination was within normal limits before and after operation. Serum lipase was normal in all (five cases) before and after operation. No conclusions could be reached here.

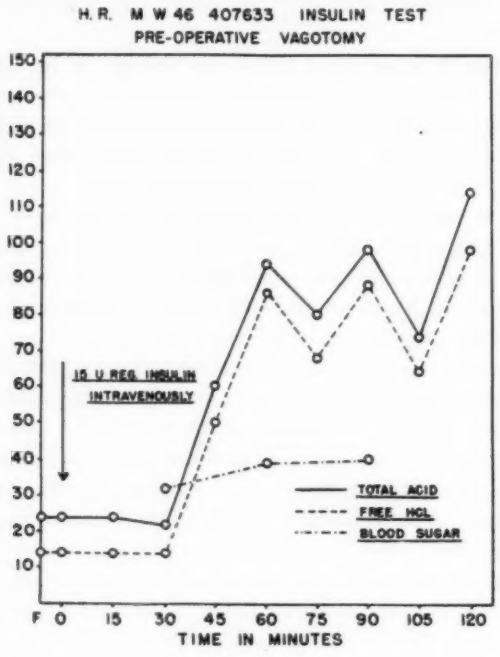
The change in bowel habit which was thought to have borne some relationship to alteration in pancreatic function by virtue of vagotomy, was indistinguishable in those with normal from those with abnormal serum amylase values. Changes in organs other than those already mentioned have not been noted or recorded to date.

V. *Insulin test:* This test was suggested by the work of Raholm (22), Ihre (23) and Babkin (24). Its purpose is to determine the completeness of severance of vagal fibres supplying the stomach. A critical analysis of it appears under "Comment" elsewhere.

It is based on the generally accepted physiological fact that hypoglycemia induced by insulin administration stimulates the vagal center in the medulla, and in turn results in stimulating both the motor (26) and secretory (22, 27) mechanisms of the stomach by way of the vagi. This phenomenon is noted in the human stomach with intact vagi (see Graph I). The resulting stimulation of gastric secretion can be abolished upon exhibition of atropine (30) or after glucose administration or epinephrine (25). The ability to detect the presence of even a few uncut vagal fibres innervating the stomach in gastric pouches of dogs by this method was shown by Jemerin, Hollander, and Weinstein (28). Based on these data, Weinstein, Colp, Hollander and Jemerin (29), and Hollander (25) devised a clinical test to determine whether any uncut branches supplying the stomach remained after bilateral vagotomy.

In order to obtain a gastric secretory response to insulin-induced hypoglycemia transmitted by the vagus nerves, the blood sugar level must be reduced to 50 mg per 100 cc. or less. After simple vagotomy operations this is usually accomplished by 15 units of regular (unmodified) insulin given intravenously, and where vagotomy is accompanied by a gastroenterostomy or subtotal gastrectomy, this is increased to 20 units in the hope of obtaining a greater outpouring of acid to off-set neutralization by regurgitated intestinal contents in both gastroenterostomy and subtotal gastrectomy and to get the maximum response from a re-

duced acid secretory membrane after the latter operation. After an over night fast, a Levine tube is introduced into the stomach and all of the gastric contents aspirated, measured and titrated for free and total acidity. Fifteen (or twenty) units of regular (unmodified) insulin is given intravenously and the time recorded. At fifteen minute intervals for two hours the stomach contents are completely emptied and the free and total acidity of each specimen are determined. Blood

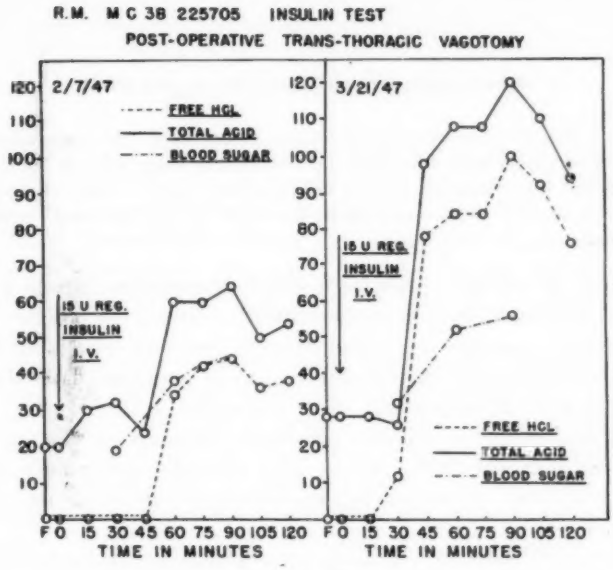



GRAPH I

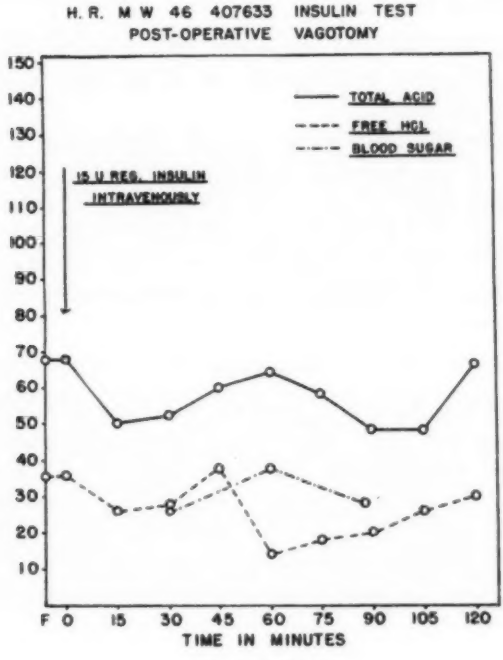
samples are taken prior to and at one-half hour intervals for one and a half hours after insulin administration.

The response is regarded as positive if there is an increase in gastric acidity after insulin administration (Graph II). This is thought to indicate that vagal innervation has been incompletely interrupted. A negative response (Graph III) is one in which there is no appreciable change in gastric acidity following injection of insulin. This is generally interpreted as evidencing complete interruption of vagal innervation to the stomach.

Gastric retention and stasis of long duration is common after vagotomy. This




GRAPH II


H. R. M W 46 407633 INSULIN TEST
POST-OPERATIVE VAGOTOMY
TOTAL ACID
FREE HCL
BLOOD SUGAR
15 U REG. INSULIN INTRAVENOUSLY
F 0 15 30 45 60 75 90 105 120
TIME IN MINUTES

GRAPH III

makes it difficult to secure uncontaminated gastric juice. We have solved this problem by giving only clear fluids for twenty-four hours prior to the test and nothing by mouth after six p.m. of the preceding night. Drugs influencing secretion or motility are also interdicted for a day prior to the test. Smoking is forbidden.

Eleven of fourteen cases with simple vagotomies (Group I) had insulin tests performed post-operatively. Three gave positive tests; the clinical response was satisfactory in two and unsatisfactory in one where a subtotal gastrectomy had to be performed later because of recurrence of ulceration. Five responded with negative tests; the clinical results in all were considered generally satisfactory. In two, the test was equivocal but with clinically satisfactory results in both to date. In one the test was unsatisfactory as was the clinical response.

In group II (bilateral vagotomy with pyloroplasty or gastroenterostomy) seven post-operative insulin tests were done; two were positive and five were negative. The clinical response was satisfactory in all.

In group III (bilateral vagotomy with subtotal gastrectomy), all were symptomless even though one of the three post-operative insulin tests was positive.

VI. *Dietotherapy:* Only where subtotal gastrectomy is performed in addition to vagotomy, are patients instructed to partake of six bland feedings daily because of the smallness of the residual gastric pouch. In the other groups there are no dietary restrictions.

VII. *Pharmacotherapy:* None was given in any instance save in an occasional bout of diarrhoea when an antispasmodic and sedative were administered temporarily.

## COMMENT

From a medical standpoint, what has been accomplished in a period of observation of a year? Final answer cannot be had because many sequelae and complications following gastric surgery appear after many years. Therefore, adequate evaluation is impossible for at least 5 to 10 years. However, it is significant that some of the advantages and disadvantages following vagotomy recorded here have appeared in about the same relationship in the experiences of Grimson

and his co-workers (18) after one and a half years, Moore, Chapman, Shulz and Jones (20, 31) up to two years, and Smith, Ruffin and Baylin (32) up to twenty-seven months.

It is to be noted that our interpretations may be at variance with our surgical colleagues (12) with whom we have studied and observed the same material. This arises from differences in approach and viewpoint.

It is quite clear to us that the most striking relief afforded by this operation is freedom from pain, heartburn, gnawing and a vague sense of nausea. Fullness is present in most instances but tends to disappear and is rarely troublesome. Patients with gastroenterostomy or pyloroplasty have fullness at the outset but to a lesser extent. These patients eat everything, three time daily, and are without psycho-, dieto-, or pharmacotherapies. Those with sub-total gastrectomy are directed to eat smaller portions of a smooth dietary about six times daily at the outset. This is necessary to avoid fullness which is greater here than in gastroenterostomy due to diminished gastric capacity. Subsequently, patients reduce feedings voluntarily to about three to five times daily.

The relative bowel frequency among all groups—one to three daily defecations in lieu of constipation—usually requires no treatment, is welcomed by the patient, and for the present remains unexplained.

In some instances severe emotional disturbances which prior to operation were usually followed by distress are experienced now without discomfort. Patients seem enthusiastic about the procedure.

### *Factors Indicating Complete Bilateral Section of Gastric Vagal Branches*

To date, the sina qua non for success to follow the operation of bilateral vagotomy, is thought to be complete severance of vagal fibres supplying the stomach. There is a striking difference of opinion as to the distribution of the gastric branches of the vagus nerve. Bradley, Small, Wilson and Walters (33) indicate a fairly constant pattern of arborization of the vagi over the lower oesophagus in 90% of cases and therefore believe the infradiaphragmatic approach is adequate. At the same time Miller and Davis (34) demonstrate numerous branches and a variety of patterns and hence advocate a supra-diaphrag-

matic section. Rienhoff (35) has pointed out that in his denervation of the lungs for asthma, fibres of the vagus nerve enter the sympathetic chain in the cervical region and are carried along in this structure to the celiac plexus from which they are distributed to the stomach as parasympathetic fibres. In addition, Osler Abbott (36) comments on the frequency with which the right vagus nerve breaks up into multiple filaments at a high level, some of which reach the stomach after a considerable course in the muscularis of the oesophagus. Thus, complete severance of vagal branches involving the stomach becomes a problem. At present, the clinician can only employ the following to determine complete section: 1) symptoms; 2) the insulin test; 3) the degree of gastric acidity and the volume of nocturnal secretion; and 4) gastric tone and motility.

1. *Symptoms:* In this entire group of cases symptoms are an unreliable guide to determine completeness of vagotomy. If the insulin test is an index of complete severance, then our results would indicate that certainly within the first year, there is no difference in the relief of symptoms between those who would appear to have complete vagal section as contrasted with those with incompleteness. In all but three instances were they relieved immediately after their operation of all distressing manifestations regardless of their responses to the test.

2. *Volume of gastric secretion:* After vagotomy there is a definite decrease (50% or more) in volume of nocturnal secretion as compared with pre-operative levels (4). In general there is a reduction of free hydrochloric acid, but this is not as uniform as the volumetric change. However, as time goes on, apparently the volume tends to resume its usual pre-operative level (20). Thus, diminished gastric secretory volume in itself can not be used as a gauge indicating complete and permanent severance of gastric vagal fibres.

It remains to be proved that an increase or decrease in nocturnal gastric secretory volume is significantly related to a positive or negative insulin test indicating partial or complete vagal section, respectively. We have evidence in two cases showing that in the face of adequate insulin-induced hypoglycemia, reduction in volume accompanies an equivocal as well as a positive test. On the other hand, a repetitiously negative insulin test may be present even though there is a gradually increasing secretory volume. Apparently gastric autonomy accounts

for this (20). Thus, again, it would appear that the decrease or increase in volume of gastric secretion per se is *no* index of the completeness of vagal section.

3. *Alterations in gastric tone and motility:* Section of the vagus nerves —complete or incomplete as judged by the insulin test— will in the majority result in profound changes in gastric tone and motility which, in large numbers, tend to revert to normality within a year. There are also some cases with apparent complete section and little or no changes in tone and motility. Thus, these changes in themselves cannot be used as a measure of completeness of vagal section.

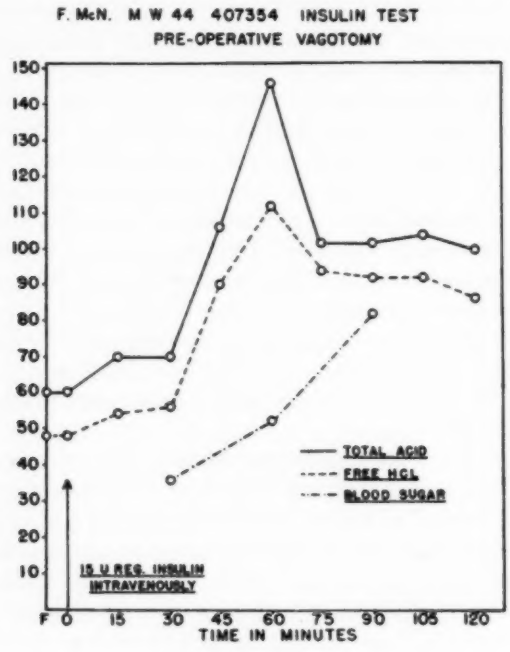
4. *Palmer acid test:* The introduction of 300 cc. of ½% hydrochloric acid into the stomach of patients with peptic ulcer causes pain (positive response). The results obtained in peptic ulcer patients following vagotomy are contradictory. For instance, Smith, Ruffin and Baylin (32) maintain that the test is negative (no pain after the introduction of acid into the stomach) following complete bilateral vagotomy; Dragstedt (37) says patients have pain following the introduction of acid after vagotomy and uses these data to indicate that the operation does not produce anaesthesia by cutting the vagus nerves. In consequence, this cannot be used to establish complete vagal section at the present time.

5. *Insulin test:* The rationale and criteria of positive and negative insulin tests as well as their meanings have already been pointed out. The insulin test, in our hands, is particularly difficult of interpretation in those either with sub-total gastrectomies or gastroenterostomies. Dilution and neutralization of gastric secretion by small intestinal contents, and, in addition, the paucity of residual secreting gastric tissue after sub-total gastrectomy, despite larger doses of intravenous insulin, account for this. Thus, the insulin test is more satisfactory in stomachs with simple vagotomies.

If the insulin test is clinically accurate, is it essential to cut all of the gastric vagal branches when freedom from disturbing symptoms, alterations in gastric tone, motility and secretion occur whether the test is positive, equivocal or negative? If these changes take place without the inviolate occurrence of complete severance as determined by the insulin test, may not the original premise of *total* ablation of all vagal branches to the stomach as a condition inherent to the success

of the operation be in error? Anatomically, there is a question whether all the vagal fibres to the stomach can always be interrupted (33, 34, 35, 36).

On the other hand, may not the interpretations to responses to the insulin test in human beings be questioned at this time? Three circumstances suggest this: a) our experience with a negative test

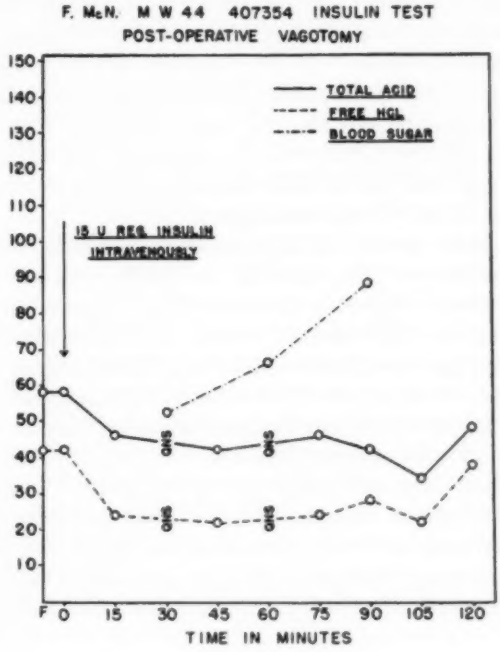



GRAPH IV

in one instance when the surgeon was certain he had not cut all of the fibres since the operation had to be terminated abruptly due to the sudden collapse of the patient (see Graphs IV and V). Criticism may be offered that the insulin induced hypoglycemia in this case measured 52 mgs. of glucose per 100 cc. instead of 50 mgs. the upper limit insuring adequate hypoglycemia. However, another technician could have read this just as easily as 50 mgs%. This patient had complete

symptomatic relief and changes in gastric tone and motility noted in those regarded as having had complete severance of vagal fibres.

b) As indicated above, in the majority there are no determinable subjective or objective differences in our hands within the first year after vagotomy operations, in those with positive, equivocal and negative tests. It remains to be established that a significant number with




GRAPH V

positive insulin tests, (said to indicate incomplete section thereby implying an unsatisfactory operative outcome), eventually fare worse than those with persistently negative tests, assuming, of course, that the tests have been properly performed.

c) While the insulin test is based on sound physiological grounds, and while it may adequately measure complete vagal section in dogs with gastric pouches, these in themselves do not necessarily mean that

complete section of the vagi can be ascertained just as effectively by this method in the more complicated human machanism. As already discussed, it may be that from a practical clinical standpoint such complete vagal severence is unnecessary, and indeed may be impossible in some instances. If so, how is the insulin test to be used in interpretation between total, adequate and inadequate vagal section? This is not to say that the insulin test should not be performed. It should be continued in the hope of eventually evaluating it properly from a clinical standpoint. It should be repeated over varying periods when negative, for if the test should become positive it would probably indicate sufficient regeneration of vagal tissue of possible clinical importance. However, it remains to be proved that a single positive insulin test in itself indicates inadequate and hence unsatisfactory vagal section from a clinical standpoint.

6. *Other criteria in establishing adequate vagal section:* They are the continued absence of pain, gnawing and heart-burn, the absence of objective evidence of gross or occult bleeding, recurring ulceration or fistula formation. The history, x-rays, determinations of gross or occult blood in gastric aspirates and in feces, as well as gastroscopy, are the methods to be employed. Serial insulin tests, particularly in those with stomachs capable of secreting adequate acids, may eventually become informative for reasons given above.

VI. *Problems Associated with Vagotomy:* A. *Pain:* The complete relief of pain afforded by vagotomy is not an unmitigated blessing. The clinician may have to develop other attitudes and new approaches to recognize recurrent ulceration, perforation and obstruction in patients whose pain sense has been obliterated or obtunded following vagal section.

B. *Gastritis—jejunitis:* Comparing our gastroscopic experiences in sub-total gastrectomy without vagotomy, it is now possible to say that bilateral vagotomy does not protect the patient from developing oedema, erosion, hypertrophy and friability in the residual gastric pouch and the attached jejunum. The former group often present themselves with various and sundry complaints and respond readily to simple measures. However, those with vagotomy and sub-total gastrectomy, during their period of observation (first post-operative year), are without complaints and appear to be in no need of any medical

management. Two questions arise. 1) Is this painlessness desirable? 2) Will these changes eventually lead to recurring hemorrhage and ulceration despite vagotomy?

VII. *Indications for vagotomy:* By virtue of our experiences to date, the following is our method of approach with regard to the selection of cases for vagotomy at this time:

1. *Intractable pain:* If intractable pain is to be defined as continuous, unremitting distress uninfluenced by combined psycho, dieto and pharmaco-therapies in those with uncomplicated duodenal ulcer (ulcer without evidence of previous perforation, gross hemorrhage or obstruction), then we must report that we have never encountered this phenomenon. Apparent intractability of distress under these circumstances is usually the result of the patient's failure to follow a prescribed routine or the inadequacy of the clinician in management. To relieve this type of patient from his complaints by merely performing vagotomy teaches him nothing. The manner in which his personality reacts to life's situations may sooner or later express itself in other organs and in other forms. Besides, this type of patient is being subjected to a 20% chance of having additional gastric surgery performed in consequence of certain sequelae and complications of vagotomy to which references have been made. Therefore, vagotomy, or any type of surgery, is not indidated—in our humble opinion—in this type of problem.

2. *Complications:* a) *Acute perforation:* The fact that 50% to 75% of cases manifesting acute perforation are said to return with varying types of distress in three to five years following suturing, makes the addition of vagotomy 10 to 14 days following this procedure a welcome addition in the hope of preventing recurrences. It must be remembered that not all of the 50% to 75% of those returning with difficulties present surgical problems. However, at the present time we are inclined to urge supradiaphragmatic vagotomy within two weeks following suturing for acute perforation.

b) *Recurring hemorrhage:* If peptic ulcer can be demonstrated as the cause and it is without obstruction, and operation is decided upon later to prevent subsequent bleeding, then simple vagotomy may be undertaken in preference to the removal of about 75% to 90% of the stomach—a sub-total gastrectomy—an operation which can be undertaken at a later date if necessary.

c) *Obstruction:* Whenever a gastroenterostomy or a sub-total gastrectomy is to be done for obstruction due to cicatricial tissue, then vagotomy may also be performed in the hope of preventing recurring ulceration, particularly in the region of the new stoma.

## VIII. SUMMARY

I. A total of 39 cases were evaluated from the medical standpoint within a year following attempted complete bilateral section of gastric vagal fibres for relief of peptic ulcer and its complications.

II. The rationale of the procedure was discussed.

III. The striking results were the relief from pain, heart-burn, gnawing and nausea in all but three, two of whom required further surgery.

IV. X-rays revealed disturbances in tone and motility in the large majority, which tended to resume some semblance of normality within a year.

V. Gastroscopic findings are recorded.

VI. The insulin test is critically analyzed.

VII. The criteria for establishing adequate vagal section post-operatively is presented since complete bilateral section of vagal gastric branches may not always be obtainable and such may not always be necessary.

VIII. The obliteration or obtunding of pain following this operation is not an unmitigated blessing.

IX. Indications for vagotomy are discussed.

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## DISCUSSION OF THREE PAPERS OF SYMPOSIUM ON VAGOTOMY FOR PEPTIC ULCER

*Dr. A. M. Harvey:* I would like to ask Dr. Grose if they have used any of the cholinergic drugs such as urocholine for their effect on motility. The vagus is a cholinergic nerve and after it is cut the stomach becomes very susceptible to the stimulating action of these drugs, and they have been found useful in controlling that difficulty which follows vagotomy.

*Dr. William Grose:* Dr. Harvey, we have had experience with the drug (urocholine). The drug has been used only while the patients were still in the hospital. In two such patients gastric motility was perfectly normal during the post-operative stay in the hospital and the patients were doing well on discharge when the drug was discontinued. One patient also showed normal gastric motility and emptying. The patient was on the drug for a very short period of time, developed side effects, and the drug was discontinued. Two days later there was seen huge gastric dilation which has persisted.

*Dr. John Eager Howard:* Are there any further questions?

*Dr. George Finney:* I would like to offer one thing for what it is worth. I don't believe that we can throw all operations on the stomach, plus vagotomy, in together and get any true evaluation of the possibilities of vagotomy or its bad effects. I would like to ask Dr. Grose about those four patients that he said were bad results from the surgical standpoint. I would like to know what other surgery was done. I would also like to know whether the vagotomy was done from above the diaphragm or below, because in my very limited experience I can't help but feel that those are very important factors. I think we ought to group our supra-diaphragmatic cases together, namely those who have no other surgery, because I believe there is much more possibility of getting all the vagal fibers by going through the chest. Then again I think we ought to group our cases done from below the diaphragm without any other procedure except vagotomy in another group and, in a third group, those where other surgery is done, plus vagotomy. Other surgeons have noted that there is a great difference many times in the results, both objective and from the patient's standpoint. I

would also like to mention two cases which were very interesting and see if anyone could perhaps give the explanation of the findings. Both cases had very definite duodenal ulcers which were quite deep. Films were made just before operation, and then were made, one in nine days and the other in ten days post-operative—done by the same X-ray man, and at this time ulcers could not be demonstrated in either of these cases. Now I can't believe that those ulcers healed in that short period after vagotomy, but I wonder what part the lack of spasm plays, and also its part in the relief of pain.

*Dr. William Grose:* Dr. Finney, one of those four cases was a man done through the chest. The operator thought the division of nerve was complete. The insulin test done after operation seemed to show a complete vagotomy. He did well for several months and then began to develop fullness and later began to develop pain which he said was similar to his original ulcer pain. He was re-explored and a definite active duodenal ulcer was found, typical grossly and microscopically. That was one failure. The second was a man who had an operation for exploration for a gastric ulcer which was biopsied and was benign on frozen section. Because he was in very poor shape, only a vagotomy was done. That was below the diaphragm. He went from good to bad, to good to bad, shape over a period of monthsa nd finally was reexplored. The ulcer seemed to have healed. He simply had dilation of the stomach, atony so severe that he could not get food through a patulous pylorus. The other two cases are two that had vagotomies and who are suffering from fullness and repeated vomiting.

As to the disappearance of duodenal ulcer very shortly after vagotomy, I can only say that it is so very difficult to get barium to fill the duodenum of these people after vagotomy it seems to me hard to evaluate the x-ray evidence of healing of an ulcer. At least, the stomach itself doesn't push barium through very satisfactorily and I suppose it would be hard to manipulate it so as to fill well the duodenum at the site of the ulcer.

(*Adjournment*)

# THE EXPERIMENTAL INVESTIGATION OF PEPTIC ULCER*

EDWARD M. HANRAHAN

*From the Department of Surgery of the Johns Hopkins University and Hospital and from the Surgical Hunterian Laboratory*

Much of our knowledge of the pathogenesis and pathologic anatomy of peptic ulcer is based on the observations of Cruveilhier (1), Rokitansky (2) and Cohnheim (3). In fact little can be added to Welch's (4) account of the subject in 1885. With more accurate medical and surgical diagnosis we have perhaps a clearer conception of its clinical incidence and psychosomatic basis. It occurs almost exclusively in man, and in about 95% of cases it occurs in a limited portion of the stomach and duodenum, that is, along the lesser curvature more often posterior than anterior, in the antrum and in the duodenum rarely below the ampulla. It is far more common in the white race and in men more than women. Its period of onset is the period of increasing ambition and responsibilities. Once an individual has shown himself vulnerable to peptic ulcer, clinical experience suggests that it may be a lifetime affliction with periods of exacerbation and remission; that the tendency to heal is opposed by some derangement, the complete nature of which we are ignorant.

Most experimental ulcers are thought to be the result of the action of gastric juice on injured mucosa. Ivy (5) points out, as did MacCallum (6), that even these two factors, injury and digestion, if unaccompanied by continuance of the underlying cause are probably insufficient to prevent healing. Berg (7) recently expressed the opinion that penetrating lesions may not be preceded by a mucosal defect but are caused by a single factor which simultaneously affects all the layers of the gastric walls.

One example of chronic ulcer produced by surgical alteration of gastric function is the jejunal ulcer which sometimes occurs after gastrojejunostomy in man and in animals. Following the demonstration by

*Although the paper was not given as part of the Symposium on Vagotomy For Peptic Ulcer, it is included here because of its pertinency to the subject at hand. The original Max Brödel drawings are herein published for the first time. —Editor.

Exalto (8) that such jejunal ulcers may be regularly produced by performing gastrojejunostomy with pyloric exclusion and draining duodenal contents into the proximal loop of the cecum, Mann (9, 10, 12) and his associates developed and modified the procedure and made exhaustive studies of this type of ulcer. Their method, which Morton (13, 15) called surgical duodenal drainage, has refocused attention on the part played by normal intact pyloric function and upon Boldyreff's (16) belief, supported by Carlson (17), Elman (18) and many others, that a high and constant gastric acidity is reduced by some neutralizing mechanism, probably a reflux of alkaline pancreatic juice which depends on normal pyloric activity. This belief was developed further by Olch (19) who looked upon the prepylorus, the pylorus and the first part of the duodenum as a single organ the function of which is that of a mixing chamber in which acid gastric contents are rendered innocuous to duodenal mucosa.

In spite of many conflicting observations, attention is directed again and again to a disturbance of normal regurgitation as one of the most important links in the chain leading to clinical peptic ulceration. There are many possibilities for central, reflex and local origins of pylorospasm which breaks up the normal mechanism with resulting faulty regurgitation leading to hyperacidity and, possibly in the case of erosions, continued ulceration. It is a well known fact that either pyloroplasty or gastroenterostomy can successfully overcome pylorospasm: pyloroplasty by entirely breaking the pyloric ring, gastroenterostomy by creating an emergency exit and means of regurgitation and abolishing spasm.

Inasmuch as pylorospasm seems to be so important in this disorder it was inevitable that the part played by the vegetative nervous system should be closely scrutinized. Furthermore its influence on the blood vessels in the usual region of ulceration should not be ignored.

Dating at least from Cammerer (20) in 1828, there have been innumerable reports of experiments involving the vagus or the splanchnic nerves and many conclusions have been contradictory. Apparently ulcers have been produced by experimentally disturbing the equilibrium of the vegetative nervous system by direct attack on either the vagus or the splanchnic nerves. In general the vagus stimulates activity while the splanchnic nerves inhibit, and the weight of evidence supports Pavlov (21) in his belief that the vagus is the main pathway

between the brain and the upper gastrointestinal tract. Greggio (22) and later Hughson (23) noted that vagus neurotomy brings about delayed motility and hypotonus of the pylorus which allows increased patency of the pyloric lumen. Beaver and Mann (24) found that in animals in which surgical duodenal drainage had been performed, ulcers developed as usual when the splanchnic nerves had been cut but did not occur invariably after section of the vagus nerves. Durante (25), as well as DallaVedova (26), found ulceration after cutting the splanchnic nerves in otherwise intact dogs. Cushing (27) suggested that hypothalamic disturbances gave rise to the stimuli which affect the activity of the gastrointestinal tract by way of the vagus nerves. Clinical application of the idea that section of these nerves might logically be tried in patients with peptic ulcer had been made by a few observers but it is Dragstedt (28) who is responsible for the present great interest in its use. His results and the results of others working along similar lines when put to the test of the sufficiently long time interval necessary in dealing with peptic ulcer may shed further light on the problem.

The following is a brief summary of one of the efforts made during the period 1920 to 1930 to throw further light on the resistance of gastric and duodenal mucosa to the action gastric juice following extensive surgical alteration of gastrointestinal continuity. These particular observations were not reported at the time (1925) because of the uncertainty regarding any inferences to be drawn from them. However, later consideration warrants the belief that this very uncertainty may in itself justify comment. The hitherto unpublished drawings by Max Brödel are further stimulus to publication.

1. *Implantation of opened segments of intestine into the stomach wall.* This was done in nine dogs. A segment about 10 cm. long taken from the jejunum or upper ileum, attached to its mesentery, was opened and implanted into a defect made just above the greater curvature in the lower fundus. Intestinal continuity was then restored.[1] The intestinal mucosa showed no ulceration in its foreign environment, even in

[1] This necessitated the use of a rapid means of intestinal anastomosis and presented the opportunity to try several different methods. One of the most satisfactory was based on the Parker-Kerr technique. Very thin-bladed clamps made for the purpose were used and a single Cushing continuous mattress suture of 000 chromic catgut, interrupted in three places, completed the anastomosis. Plate 4 illustrates a healed anastomosis with the suture line scarcely visible.

those few instances where silk sutures had penetrated the lumen. In two dogs the patch had puckered into a pouch which contained stones, bones, etc. In these there were superficial erosions which did not penetrate beyond the mucosa (Figure 1 and Plates 1, 2 and 3).

This procedure was first used by Katzenstein (29) and has been repeated by many others (11, 14). When ulcers have been found it was suggested they may be due entirely to nutritional disturbances resulting from inadequate circulation (Hotz) (30). This may account for the ulcers encountered by Morton (15) and de Takats and Mann (31) in patches implanted on the lesser curvature. In this position the

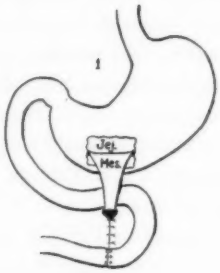


FIG. 1.

blood supply through the mesenteric pedicle may well be impaired by pressure of the animal's stomach. Morton (15) carried this procedure a step further and found ulceration in the patches when Mann's surgical duodenal drainage was also done. It is interesting to note that Andrus, Lord and Stefko (32) found a diminution of gastric acidity following patch implants and used this procedure in the treatment of clinical peptic ulcer.

2. *Stomach flaps reimplanted into gastric-wall.* This was done to compare the healing with intestinal implants. Large flaps were made and the pedicle narrowed down practically to a single artery and vein. Not until these vessels were of no appreciable size was there any evidence of susceptibility of the gastric mucosa to erosion or ulceration. Figure 2.

3. *Attempts to convert the stomach and first part of the duodenum into a single pouch.* Figures 3, 4 and 5 illustrate the methods used. Only

one dog in which the operation shown in Figure 3 was done lived as long as ten days. That dog was killed in a dog fight. The mucosa was intact. Four other dogs died within three days of rupture or perforation near the blind end of the duodenum.

The procedure shown in Figure 4 was done in two dogs. One died on the fourth day with no cause evident at autopsy. The other dog

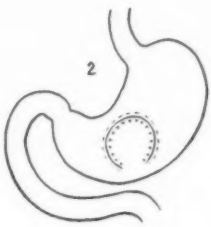


FIG. 2.

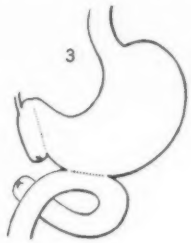


FIG. 3.

FIG. 4.

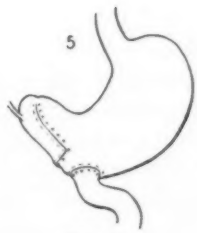


FIG. 5.

died after three weeks of mange and inanition. The mucosa was everywhere intact.

Figure 5 illustrates the operation done on three dogs. Two dogs died on the third day of perforation or rupture of the duodenal flap. The third dog died on the fourth day of no discernable cause and in this dog the mucosa was intact.

4. *Diversion of bile to mid-ileum by cholecyst-ileostomy and division of common duct. Conversion of stomach and descending duodenum into a single pouch by a long Finney pyloroplasty.* Three dogs were used. One

dog died during the first 2 hours. Two dogs remained in good condition 8 and 10 weeks respectively. At autopsy the mucosa was everywhere intact (Figure 6).

5. *Modified Exalto (Mann-Williamson) procedure. Surgical duodenal drainage by pylorectomy, drainage of descending portion of duodenum into mid-ileum and anastomosis between stomach and remaining duodenum* (Figures 7, 8 and 9).

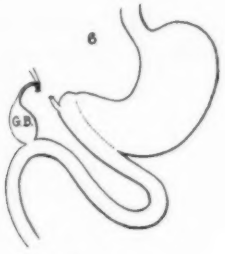


FIG. 6.

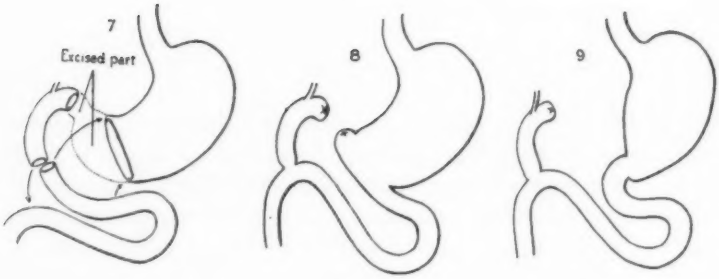


FIG. 7. FIG. 8. FIG. 9.

This procedure, with variations has been used by many investigators. Four dogs survived this operation for at least 24 hours but three in which end-to-side anastomosis was done died before the fourth day because of perforations in the duodenum near the suture line. One dog, end-to-end anastomosis, died on the 28th day of inanition. The mucosa was intact.

6. *The Chlumsky* (33) *procedure. Pylorectomy, with drainage of duo-*

*denal contents into upper portion of stomach. Side-to-end gastrojejunostomy* (Figure 10). This operation was done on three dogs. All survived for at least two months, and all showed chronic ulcers in the afferent loop of jejunum (Plate 5). One dog was sacrificed after three months during which time the interior of the stomach had been observed at intervals gastroscopically. By this means the retarded healing of the lower gastro-jejunal anastomosis was seen.

This surgical arrangement seems to be the antithesis of the Exalto procedure since duodenal contents are drained toward rather than away from the stomach. Ulcers follow the use of either procedure but in my

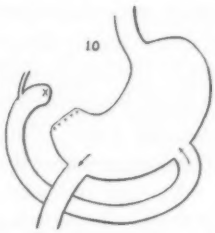


FIG. 10.

hands at least, the Chlumsky procedure gave rise to chronic ulcers as contrasted to the acute perforating ulcers of the Exalto procedure, although Mann and Williamson found chronic ulcers in a high percentage of their animals. This operation was tried by Kelling (34) and later by McCann (35) with similar results. McCann found jejunal ulcers in 80% of his animals and emphasized the importance of the mechanical factors involved, as had Mann and Williamson. This point of view was not shared by Steinberg and Proffitt (36).

The inferences to be drawn from observations following procedures such as these are at best not clear and they are frequently contradictory. It would appear that gastric mucosa is resistant to injury as a result of cutting down but not completely blocking its circulation. Intestinal mucosa with intact circulation is likewise resistant to the effect of a gastric environment when implanted as a patch in a defect of the stomach wall. Morton found this to be a relative resistance and affected by concomitant surgical duodenal drainage. The absence of

bile from the upper duodenum is not conducive to duodenal ulceration in the presence of a wide opening between the stomach and duodenum. Others, notably Grey (37) and Elman (38) have shown that the absence of pancreatic juice is of importance. Surgical duodenal drainage to the lower ileum is as shown by Exalto, Mann and Williamson, and others, a procedure which is followed by a high incidence of ulcers in that portion of the intestine used to restore gastrointestinal continuity. This might well imply that the absence of upper duodenal secretions is the factor which renders intestinal mucosa sensitive to the effect of gastric juice were it not for the fact that complete backward diversion into the stomach (the Chlumsky procedure) is also followed by ulceration.

There are apparently factors other than simple mechanical neutralization which are involved in the production of peptic ulcer by these extensive surgical procedures. Such procedures are usually followed by marked disturbances in the dog's nutrition and it is well known that ulceration is common in cachectic dogs. This comment may well be directed toward other extensive experimental surgical procedures not included in this discussion. Perhaps the most direct conclusion to be drawn from these and other similar reported experiments dealing with the part played by digestion in the production of chronic peptic ulcers is that the mechanism which makes digestion locally effective has not been fully explained.

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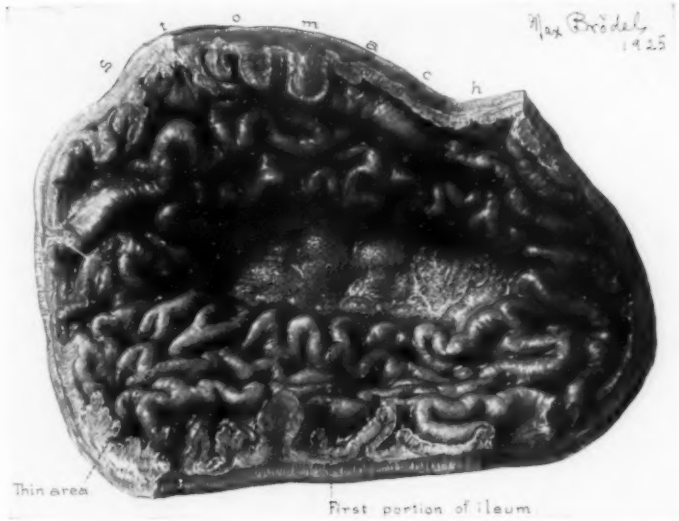


PLATE 1. ANTERIOR WALL OF STOMACH, POST-MORTEM FORMALIN FIXATION
The "thin area" proved on microscopic examination to be a mucosal erosion.

PLATE 2. THREE INTERRUPTED SILK SUTURES HAVE PENETRATED THE LUMEN, WITH NO RESULTING ULCERATION.

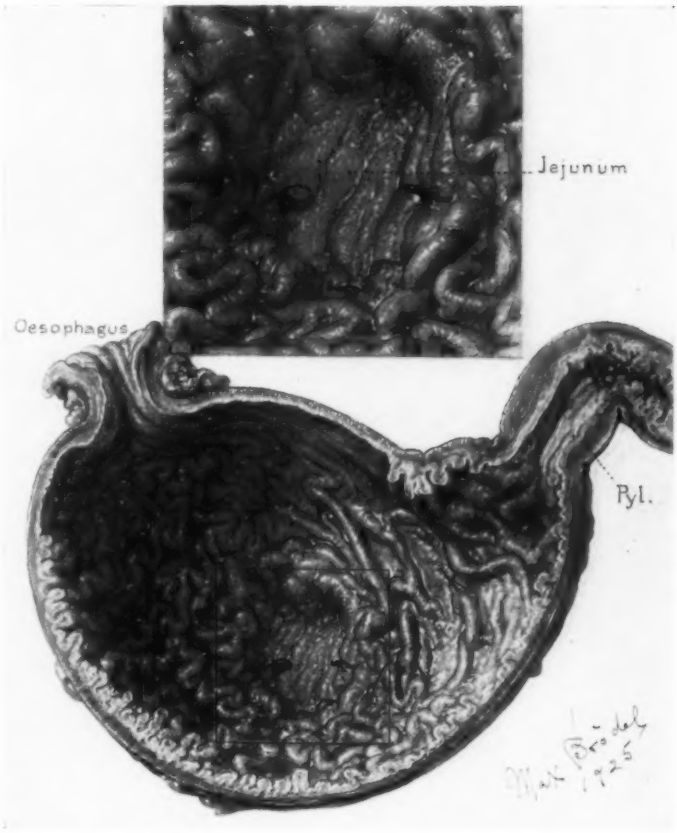
Jejunum
Oesophagus
Pyl.

PLATE 3. GASTROSCOPIC EXAMINATION OF THE INTESTINAL PATCHES WERE MADE AT FREQUENT INTERVALS BY DR. EDWIN N. BROYLES

The intact mucosa was clearly visible.

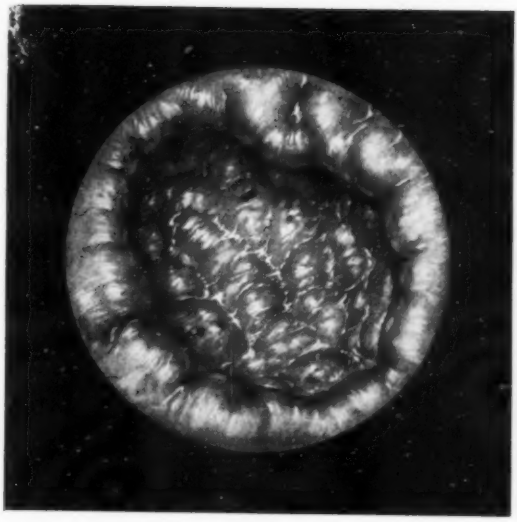

PLATE 4. HEALED END-TO-END INTESTINAL ANASTOMOSIS. PARKER-KERR TECHNIQUE.

PLATE 5. ULCER IN AFFERENT LOOP OF JEJUNUM FOLLOWING CHLUMSKY PROCEDURE

OF MICH.

# PROCEEDINGS OF THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

## Held in Hurd Memorial Hall, Monday, March 10, 1947

*Diphtheritic Polyneuritis.* Dr. George D. Gammon (Department of Neurology, University of Pennsylvania).

Shortly after the end of the European war the author had the opportunity of studying a group of cases of multiple peripheral neuritis among American, British and German troops in the Mediterranean Theatre. The largest number examined (75) were among German personnel. The cases could be classified on clinical grounds into postdiphtheritic palsy, postinfectious neuritis, sulfonamide neuritis, serum neuritis, and a group not readily identified as to cause. The preponderance of cases was due to diphtheria. After the clinical classification was made, cultures of nose and throat for diphtheria were made and blood drawn for antitoxin level determination as described by Dr. Schoenbach.

The clinical picture of diphtheritic neuritis can be readily recognized in its typical form. After nasopharyngeal infection, palatal palsy is followed by paralysis of accommodation and by the slow development of tingling and weakness of the limbs. Although motor weakness and reflex loss may exceed the sensory impairment, blunting or actual loss of cutaneous and deep sensation occurs.

The slow time course of the process is a characteristic feature which clearly distinguishes diphtheritic neuritis from the sulfonamide and the serum group, as well as some of the cases described by Guillain.

A few cases of skin diphtheria were studied, but none were seen at the time of open ulcers. The prevalence of carriers raises the question of secondary infection of skin lesions rather than primary involvement.

*Laboratory Studies on Diphtheritic Polyneuritis.* Dr. Emanuel B. Schoenbach (Department of Preventative Medicine, School of Hygiene).

Many cases of polyneuritis had been observed among the Armed Forces in Italy during 1944 and 1945. Because of a high spinal fluid protein unassociated with an increase in cells, these neuritic cases were classified as Guillain-Barré syndrome.

Review of many of the case histories suggested diphtheritic infection as the likely etiologic cause for the polyneuritis. During the summer of 1945 seventy cases of peripheral neuritis in one area were studied. A detailed history and comprehensive neurological examination of each case was undertaken and all available laboratory data was reviewed. It was found that the cases could be subdivided clinically into characteristic groups. They were:

1) Typical postdiphtheritic neuritis (42)
2) Sulfonamide neuritis (methyl sulfathiazole, Uleron) (13)
3) Postinfectious neuritis with severe general sepsis (6)
4) Unclassified atypical neuritis (9)

Laboratory investigation consisted of nose and throat cultures for *C. diphtheriae* on two successive days, employing several types of media for isolation, and quantitative titrations of the serum antitoxin levels. These laboratory studies were extended for control purposes to include 112 individuals without recent history of sore throat or polyneuritis and 17 cases of known convalescent pharyngeal diphtheria.

The results of the laboratory study may be summarized as follows:

1. Virulent *C. diphtheriae* was isolated from 52.6% of those convalescent from acute diphtheria (4–8 weeks after onset); from 17.0% of the normal control group, and 12.0% of those classified as diphtheritic polyneuritis.

2. The antitoxin content of the serum was lower among the postdiphtheritic polyneuritic and convalescent diphtheria groups than among the control group. 50% of the former groups had levels below 0.01 units of antitoxin as compared to 22% among the control asymptomatic group. This difference was essentially unchanged when less than .0025 units of antitoxin was employed as a basis for comparison.

3. Examination of the strains of *C. diphtheriae* for mitis, gravis, intermedius, etc. revealed no distinctive type characteristic which could be employed to distinguish *C. diphtheriae* isolated from cases of diphtheria, polyneuritic cases or the healthy control group.

The cases of diphtheritic polyneuritis were distinctive on clinical grounds. Laboratory confirmation of undiagnosed diphtheritic infection preceding the onset of the polyneuritis was unsuccessful. The high incidence of diphtheritic infection in the community, the relatively small number who manifest overt clinical disease, the late onset of postdiphtheritic polyneuritis, and the poor antibody response following the disease make such retrospective laboratory diagnosis difficult in diphtheria.

*Dr. J. E. Howard:* It is somewhat encouraging to the doctor to find that the specialists have difficulty in interpreting the etiological agent when they are confronted with patients with peripheral neuritis. This is a pretty broad subject and we have with us tonight a very distinguished visitor. I would like first to ask his comments on the subject of tonight's presentation—Sir Charles Symonds.

*Sir Charles Symonds:* I have listened with interest to the contributions that have been given tonight. Dr. Gammon has presented us with a very clear and convincing picture of the clinical aspects of diphtheritic polyneuritis. I am sure he is right and that the clinical picture is one that, as a rule, deserves a positive diagnosis of its own right, even if there is no positive test available. When there occurs the typical sequence of palatal paralysis and then, after delay, the polyneuritis is present, there can be little doubt about the typical clinical diagnosis, but, as he has pointed out to us, the palatal paralysis and ciliary paralysis may occasionally be absent and then we are faced with a polyneuritis which hasn't got a whole lot of diphtheritic polyneuritic characteristics. Now, we have got to note

also that the delay between the time of the infection—the time the culture is positive—and the development of the polyneuritis may be quite a long one. In these cases I noticed one in which the interval was of twelve weeks. Intervals longer than that have been recorded. In one of the cases seen in Palestine during the recent war, the interval between positive culture and the first symptoms of polyneuritis was 149 days. Now, this carries to the clinical neurologist a real lesson. When he meets with a case of polyneuritis of obscure etiology he should always think of the possibility of a diphtheritic polyneuritis, even if the history of palatal and ciliary paralysis is not forthcoming, and look for the history of sore throat or possibly cutaneous sore away back in the story, even as long as three or four months.

In regard to the Guillain-Barré syndrome—Guillain and Barré thirty-one years ago made an important contribution to knowledge when they observed that in certain cases of polyneuritis there might be a high protein in the spinal fluid without any pleocytosis. It so happened that the group of cases which engaged their attention was one with particular clinical features. During the first World War in France in 1916 and 1917 there was quite an outcrop of cases which were described by Holmes independently in 1917 under the title of acute infective polyneuritis. Holmes gave a very vivid and clear picture of that disease, with its bilateral facial palsy, rather marked developments, severe involvement of the proximate muscles and relative escape of sensory nerve fibers. He, too, observed the increase of protein in the cerebrospinal fluid. But, as Dr. Gammon has remarked, and others before him, we have since learned that in many other varieties of polyneuritis this same picture may be found in the cerebrospinal fluid. In fact, the syndrome described by Guillain-Barré is not specific for the disease in which they were interested at that time. Further than that, in the disease which was described by Holmes, and in which Guillain-Barré found this picture in the cerebrospinal fluid, we know now that, in addition to the high protein, there may be a high cell count. Dr. Gammon gave us a quite typical example of acute infective polyneuritis in which the protein content was 150 milligrams and in which there was also a cellular increase. So I think it is about time that we cease to think in terms of the Guillain-Barré syndrome. I think it is an excellent piece of scaffolding which we should now be prepared to tear down when the building is a little more completed. The tendency to think in terms of a disease, and to think that that disease was discovered by Guillain-Barré, and that it comprised an acute infective polyneuritis with a specific type of cerebrospinal fluid which isn't encountered in other types of polyneuritis, is quite wrong. I think it would be better if we just recognized the direct characteristics of that polyneuritis and that in any of them, including diphtheritic, we may find this curious syndrome in the spinal fluid.

*Dr. H. M. Thomas:* Dr. Howard, I felt as I listened to the papers that perhaps I would be pressed into service tonight under somewhat false pretenses because I really saw very little of the disease that has been discussed tonight, diphtheritic polyneuritis. I think perhaps Dr. Harvey saw the cases that we had in the Pacific

more concentratedly than anyone else in the general hospital where a group of cases were studied representing various forms of neuritides and the diagnosis of diphtheria was considered in each one. I believe that possibly he would be willing to tell us about that relatively small group.

I was interested in another aspect of the talks tonight. In contemplating the diagnosis of diphtheritic polyneuritis, it seems important that diphtheria should be prevalent in the community. When I went out to the Southwest Pacific I stopped on the way in the Central Pacific and in the South Pacific, and in each place was told of the fact that they were finding cutaneous diphtheria, and that they couldn't find it merely by the ordinary culture methods on Löffler's Media, but special cultures and procedures were necessary, so we were forewarned, and all through New Guinea we looked for cutaneous diphtheria. We didn't find any until suddenly, almost simultaneously, at Hollandia and Finschhafen, there were three outbreaks of clinical pharyngeal diphtheria. These were carefully studied and two of them were found to have been connected with the skin ward of the hospitals where they broke out. In culturing the cases—all the cases on the skin ward in those hospitals—it was found that a number of them were suffering from cutaneous diphtheria, not only in ulcers but in other eczema-like types of skin lesions. In retrospect, however, following these outbreaks, it seemed to us fairly clear that we hadn't been seeing any diphtheria before because there had been no recognized pharyngeal diphtheria. I think a very few cases of peripheral neuritides eventuated from these outbreaks The picture changed in the Philippines and there, suddenly, an outbreak of virulent poliomyelitis developed and four out of five first cases died in November of 1944. The fear was that we were encountering Japanese B encephalitis, or some other form of very virulent virus disease. The study of that is another rather long story and it only can be mentioned here to say that there were two groups fighting on the island of Leyte, the group around Tacloban and Palo, and the group farther south, and there were two different forces that came into these two areas. One came up from New Guinea and the other had come in from the Central Pacific from Hawaii. Simultaneously poliomyelitis broke out in these two areas. These outbreaks were very different because of the first seventeen cases in November and December in the Tacloban area eleven died, whereas of a comparable nineteen cases in the Dulag area only one died. In reviewing the cell count of the spinal fluid it was found that in the virulent group no case had fewer than 500 cells in the spinal fluid, and many had over 30,000 cells; whereas in the other group many had cell counts under 50 and around 20, 16, 7, 8, 4, etc. The one case that died in the Dulag area had 347 cells on the first count. It seemed that we were seeing two outbreaks almost identical clinically in that there was rapid paralysis often of an ascending variety. Subsequent review, however, indicated that the troops came from different staging areas and brought with them different diseases, namely poliomyelitis and Guillan-Barré syndrome, which simultaneously produced epidemics in the Leyte Island campaign. These cases differed from the diphtheritic group in that they came in to the hospital

complaining of severe headache and pain, and very promptly within the next few days, or a week, became seriously ill or died of an ascending form of paralysis with a bulbar lesion. No clear clinical differentiation was made at the time and battle conditions made it impossible to study thoroughly the spinal fluid albumin content. There were some sensory disturbances. Some of the patients went back to general hospitals in New Guinea and were studied later and found to have high spinal fluid proteins long afterwards, but so also had the late poliomyelitis cases. I think our experience then was not comparable to that of the Mediterranean group, but was also extremely interesting in that many forms of neuritides do occur. The bedside differential diagnosis is quite difficult, as has already been said, and these various clinical pictures should be borne in mind.

*Dr. Howard:* Dr. Baker, would you care to make a few remarks?

*Dr. B. M. Baker:* I listened with great admiration to the reports of the comprehensive studies upon neuritis made in the Mediterranean Theatre and I am sorry that I have no report of comparable importance to make on experiences with the Armed Forces in the Pacific. Dr. Thomas has indicated that in the Pacific we very soon began to see patients with peripheral neuritis of obscure etiology. The first progress was made when it was recognized that a good many cases of peripheral neuritis developed following unsuspected pharyngeal diphtheria.

There was nothing very unusual about the type of neuritis we encountered. I will confine my remarks largely to the importance of skin diphtheria as a dangerous source of infection.

Many soldiers who were evacuated from forward areas to hospitals in the rear had a wide variety of skin lesions. These lesions frequently had the typical characteristics of tropical ulcers or desert sores. Bacteriological investigation soon emphasized the importance of skin diphtheria. The importance of cutaneous diphtheria has been previously recognized both in civilian practice and in the military forces. Walsh pointed out the relationship between cutaneous diphtheria and neuritis.

In our experience careful studies were made upon 700 odd cases of tropical ulcers in a rear area where there were adequate facilities for thorough bacteriological investigation including virulence tests. One hundred ninety of these 700 cases of tropical ulcers were found to harbor toxigenic diphtheria. From these 190 cases 13 cases of peripheral neuritis were detected. It is worth mentioning that the latent period between the onset of skin infection and neuritis in these cases varied from three to six months, in contrast to the shorter period in which neuritis follows pharyngeal diphtheria. The neuritis was usually confined to the extremities. In general it was mild. Interest centered largely in epidemiological considerations and a number of studies upon natives were carried out. There was a high incidence of cutaneous diphtheria in the natives, and secondary infection of yaws and other common skin lesions constituted the chief hazard. There was a surprisingly low incidence of diphtheria susceptibility in adult natives in whom nasopharyngeal

diphtheria is apparently very uncommon. This finding emphasized the probable importance of skin infections among natives as the source from which our troops derived this infection.

*Dr. M. C. Pincoffs:* Dr. Howard, I have very little to contribute to this discussion as far as experience in the field with diphtheria is concerned. I am mainly filled with regret that in the theatre in which I stayed for some time we undertook nothing in the way of such a careful and valuable study as that which has been presented to us this evening. I found it most instructive and helpful in clarifying some ideas on this subject.

The demonstrated frequency of albumino-cytological dissociation in the spinal fluid of patients with diphtheritic infection naturally raises the question as to whether the clinical cases described by Guillain-Barré were likewise of diphtheritic etiology.

Cases seen in civilian life prior to the war usually had somewhat different clinical features from those described by Dr. Gammon this evening. The onset was frequently abrupt, the spread of muscular weakness rapid, facial diplegia common and fatal involvement of the respiratory musculature not infrequent. The spinal fluid characteristically showed no increase of cells and marked increase of protein. Diphtheria was not suspected in these cases. In view of the variance of clinical features it seems quite probable that diphtheritic infection may be only one of several etiologic agents which may produce central nervous system lesions accompanied by the changes in the spinal fluid described by Guillain-Barré.

*Dr. Howard:* Are there any further comments or questions?

*Dr. P. H. Long:* Yes, I would like to make a comment, Dr. Howard. These two reports have interested me very much because about two years ago this time I was burning up the wires trying to get some people over to study this problem in Italy; while it was not a pressing problem it was an extremely interesting one. Twenty-two months ago Dr. Gammon and Dr. Schoenbach arrived. Tonight I have heard their reports for the first time. We asked them over to study these diseases for us and I find they had to study them in the camp of the enemy, which is very much like the Army. But to become serious—the history of polyneuritis in the North African and Mediterranean Theater is rather interesting because the first time that it came to our attention was in January 1943 when we had an outbreak of eight or nine cases of a rapidly ascending paralysis in troops in the Casablanca area. Most of these men died rather promptly, and because of the fact that there were only evacuation hospitals in that area the bacteriological studies were not very complete. There was relatively little recognized clinical diphtheria in M.N.T.O. and M.T.O. Recognition was good in the North African and Mediterranean Theater. We had very little recognized diphtheria through 1943 and not until January 1944 did we get much diphtheria. This isn't so difficult to under-

stand when you realize that our troop strength up to that time was comprised of regular Army divisions who had been mobilized and in training since 1940. They had trained all over the United States and we probably had a fairly high percentage of immune troops among them. Late in 1943 we began getting in our terrific drafts of replacements, many of whom were boys who had been in the Army only eight or nine weeks and had only been away from their homes for about that length of time. Through 1944 we began to get a rise in clinical diphtheria and the problem of infectious polyneuritis first arose as a diagnostic problem in late December 1943 and in January 1944. I had seen a fair amount of diphtheritic polyneuritis in the British hospitals which followed clinical nasopharyngeal or pharyngeal diphtheria, but the thing which characterized many of our early cases of polyneuritis and which puzzled me were the people who did not have a history of clinical diphtheria, and in whose cases one could go back to his surgeon who remembered that the patient's throat was a little red ten weeks before. These people did not have what you and I would call clinical diphtheria, but eight or ten weeks later developed a type of polyneuritis. In the summer of 1944 in American and British hospitals there were instances of a rapidly progressing generalized polyneuritis which involved the face, with a spinal fluid protein of 115 to sometimes 800 milligrams per cent and which would clear up with great rapidity. I am quite sure it wasn't poliomyelitis, but at the present time I am not sure what it was. The disease fitted the description of the Guillain-Barré syndrome. Unfortunately there was not time for Doctors Gammon and Schoenbach to study them because when they came over redeployment was being carried out, and they were sending home everyone from our hospitals who could go on two legs. Thus they did not see most of the cases which we had hoped they would see because many of them, there, in January 1945 had been sent home and they had to study the reservoir of German cases at Merano.

There is one point I would like to end up on. I was brought up in the school of the South Department at Boston where the chief of the infectious service, Dr. Place, used to tell us to figure out how much antitoxin you should give a patient with diphtheria so as to cover his entire needs, then to give him twice as much. In the North African-Mediterranean Theater the directive read—not a request but a directive which said "*You will give*"—that a mild case of diphtheria should receive 60,000 units, a moderately severe case 150,000 units, and a severe case 250,000 units. I cannot say whether that had anything to do with decreasing the incidence of neuritis in patients with clinical diphtheria, but the fact remains that we appeared to have less post-diphtheritic neuritis than did the British Forces. Initially the British War Office required 24,000 units of antitoxin every twelve hours until 96,000 units had been given in diphtheria. I have had a great many arguments about that with Hysmann of the British Medical Service concerning this low dosage. Finally, in February 1945, the British increased their dosage of antitoxin in hopes of cutting down the incidence of post-diphtheritic neuritis.

*Dr. A. M. Harvey:* There has been a great deal of very interesting discussion on subject of polyneuritis. We saw various neurological conditions over a period of the three years in the Southwest Pacific and there, in a great number of them, along with the cases of polyneuritis, we saw many more cases in which one single peripheral nerve was involved, commonly the peroneal, more frequently the axillary, and less frequently one long thoracic nerve. At the same time we saw a much greater incidence of polyneuritis, much greater than one ever sees in a civilian population. I would like to ask Dr. Gammon and Dr. Schoenbach whether they saw any cases of that type along with the ones they examined with the multiple involvement.

*Dr. Gammon:* We saw two cases, more or less in passing, of shoulder girdle paralysis. One of them was American and the other British. I don't think we examined the American. We didn't have a chance to examine these patients, but the British patient had an atrophy of the shoulder girdle through the deltoid and supraspinatus. This was painless in his case. The man woke up one morning paralyzed in those muscles and this persisted for six months. The other man had had pain in his shoulder, but, as I said before, we never saw him. He was supposed to have a winged scapula. In the group we encountered I never saw a unilateral peroneal paralysis at all. Were the cases that you described comparable to those of Spill and Alvern and Fox?

*Dr. Harvey:* Yes, they were. We saw in the beginning very many of these cases of polyneuritis, the patients having old healed pigmented ulcers on the skin. You could not prove they had ever had diphtheria. We saw a good many of them develop under constant observation in the tropics. They had the clinical symptoms of pharyngeal diphtheria and no cutaneous lesions, and predominantly the great number showed involvement of a single nerve with no elevation in serum protein. The large majority that we saw had a fairly rapid onset and very characteristically the proximate muscles, particularly those along the shoulder girdle and pelvis, were more prominently involved. In almost no instances did any of these present any objective findings or any clinical nervous symptoms whatsoever. We saw a great many of those cases that Dr. Thomas described after the acute stage, when they had been convalescent for periods of up to four weeks. They were quite indistinguishable from Guillain-Barré syndrome of multiple paralysis with very little sensory disturbances and no marked elevation of the spinal fluid protein.

*Dr. H. A. Howe:* Could they have been poliomyelitis observed late?

*Dr. Harvey:* They probably were, but the question came up at the time as to whether or not, in a situation of that type, there may have been more than one specific type of nervous system virus active. Our knowledge is very superficial as to that type of disturbance. One group seemed to produce the clinical picture

of poliomyelitis and in the next group you might find the clinical picture associated with the Guillain-Barré syndrome. We still have a great deal to learn of peripheral neuritis and I would like to hear some discussion on it.

*Dr. Thomas:* I would like to ask Dr. Gammon a question as to whether some of the cases might have been poliomyelitis. There is now a study going on of some 52 cases that died of clinical Guillain-Barré syndrome, whatever that may be, and I am told by Major Haymaker in the Army Institute of Pathology that the pathological picture is entirely different from the picture of anterior poliomyelitis. Pathologically 2 of his 52 cases of Guillain-Barré came from our series, we did a number of autopsies also on cases that we felt sure were poliomyelitis, and they are very different pathologically. Our experience favors the concept of at least two distinct neurotropic viruses.

*Dr. Howe:* Just on the other side of the picture, I might say that recently Dr. Paul has isolated virus from the stools of some of the patients from the Philippines and Japan who had this vague syndrome. Needless to say, there was no paralysis at all upon which they ever felt it was justified to make a diagnosis of poliomyelitis. Yet the polio virus was actually isolated from the stools, which would certainly indicate that poliomyelitis was probably commoner in those theaters than generally recognized.

## Held in Hurd Memorial Hall, Monday, April 14, 1947

*A Report on Observations Relative to Paroxysmal Cold Hemoglobinurial.* Dr. Philip F. Wagley and Dr. William H. Zinkham (Department of Medicine).

Five groups of experiments were carried out in the study of certain aspects of paroxysmal (cold) hemoglobinuria. The subjects were two young colored patients admitted to the hospital for treatment of syphilitic infections. Both gave histories of dark urine following exposure to cold. The Donath-Landsteiner tests were positive.

The first group of experiments dealt with the fixation of the hemolysin and complement. The second studied the effect of $CO_2$ on hemolysis under specified conditions in vitro. The third consisted of observations on the influence of carbonic anhydrase inhibitors in this hemolytic system. The fourth dealt with the possible modes of action of certain hemolytic inhibitors. The fifth group of experiments demonstrated that definite morphological changes of the erythrocytes occurred prior to hemolysis. The materials and methods employed were described.

The observations suggested that hemolysin and at least one component were absorbed in the cold by erythrocytes. In the absence of complement hemolysin was not absorbed in one case. A thermolabile fraction of complement was necessary for the warm phase of the Donath-Landsteiner reaction. Under specified

in vitro conditions $CO_2$ seemed to effect the hemolytic system in one case and not in the other. This $CO_2$ effect was itself subject to the influence of temperature. Sulfanilamide and cyanide inhibited the Donath-Landsteiner reaction in one case and not in the other. These substances did not destroy complement or hemolysin under the circumstances of these experiments. Apparently they did not prevent the union of the hemolysin-erythrocyte complex in the cold, but prevented the effect of such a union. If not present during this union sulfanilamide and cyanide did not prevent the hemolysis. Under specified conditions sulfanilamide and cyanide did not prevent the effect of the thermolabile component of complement in the warm phase of the Donath-Landsteiner reaction. The inhibition of these substances was reversible. During the cold phase of the Donath-Landsteiner reaction practically all the cells remained biconcave. Spherocytosis occurred during the warm phase of the Donath-Landsteiner reaction and preceded hemolysis. By employing three different methods (ocular micrometer, optical density method of Jacobs, phase difference microphotography) no definite evidence was obtained that the cell increased in volume prior to hemolysis.

It is of interest that in these two cases, presenting clinically the same disease entity, certain observations relative to $CO_2$ and hemolytic inhibitors suggested the possibility of fundamental variants in their pathogenesis. These differences may account partially for the conflicting data reported in the literature from studies by other workers.

*Dr. Rich:* I might ask one question. The paper was very enlightening, but I would like to ask Dr. Wagley about the effects of cyanide. I didn't get that very clearly in my mind. If cyanide or sulfanilamide is added to the cells alone and then washed off will it have an effect or does it have to be present together with the hemolysin in order to have an effect?

*Dr. Wagley:* They have to be present with the hemolysin at the time of chilling.

*Dr. Harvey:* I would like to ask if there is any difference in response to antisyphilitic treatment as far as this hemolytic system is concerned.

*Dr. Wagley:* Dr. Mackenzie has had the most experience in this condition. He has stated that a study of those cases with paroxysmal hemoglobinuria who have been treated and subsequently had attacks over a long period of time did not have adequate therapy. However, there are cases in which attacks have lasted for a period of two years after antiluetic therapy. Whether there is any difference in the responses of these two types of cases to treatment cannot be answered with the present information.

*Dr. Harvey:* Has the hemolytic system been altered in any way by the treatment?

*Dr. Wagley:* It has not in its response to $CO_2$. However, one of the cases has been out of the hospital only two weeks. What changes, if any, in the qualities of the system may ensue is not predictable.

*Dr. Howard:* Is there any further comment? If not, we will go on to the next papers which comprise a unit and will be discussed together. It will be a symposium on the experiences with vagotomy for peptic ulcer.

The symposium is published in this issue.